VOLUME 1 • OCTOBER 1959 • NUMBER 4

A.M.A. ARCHIVES OF NEUROLOGY

The Cerebral Hemispheres and the Highest Integrative Functions of Man
Loring F. Chapman and Harold G. Wolff

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Robert L. McLaurin, John W. Devanney, Eugene B. Elam, and Richard B. Budde

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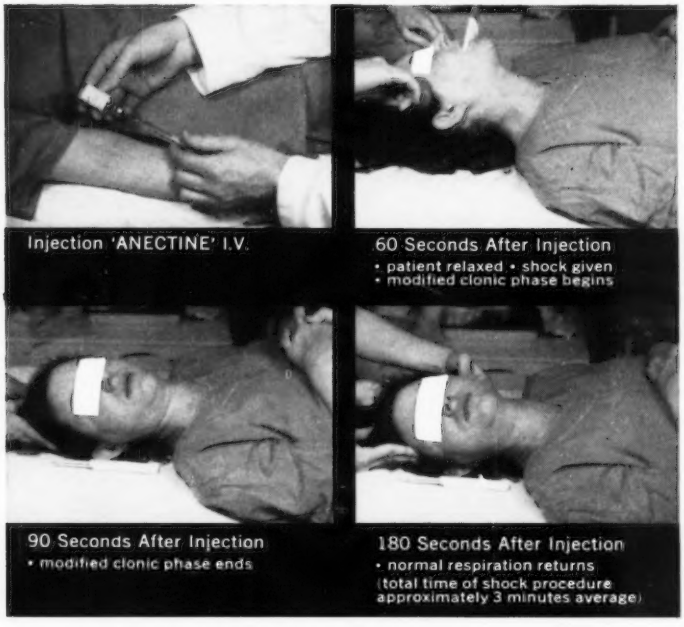
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Michael, K. D., and Wunderman, D. C.: J. Nerv. & Ment Dis. *126*:535 (June) 1958.

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Robie, T. R.: J. M. Soc. New Jersey *52*:82 (Feb.) 1955.

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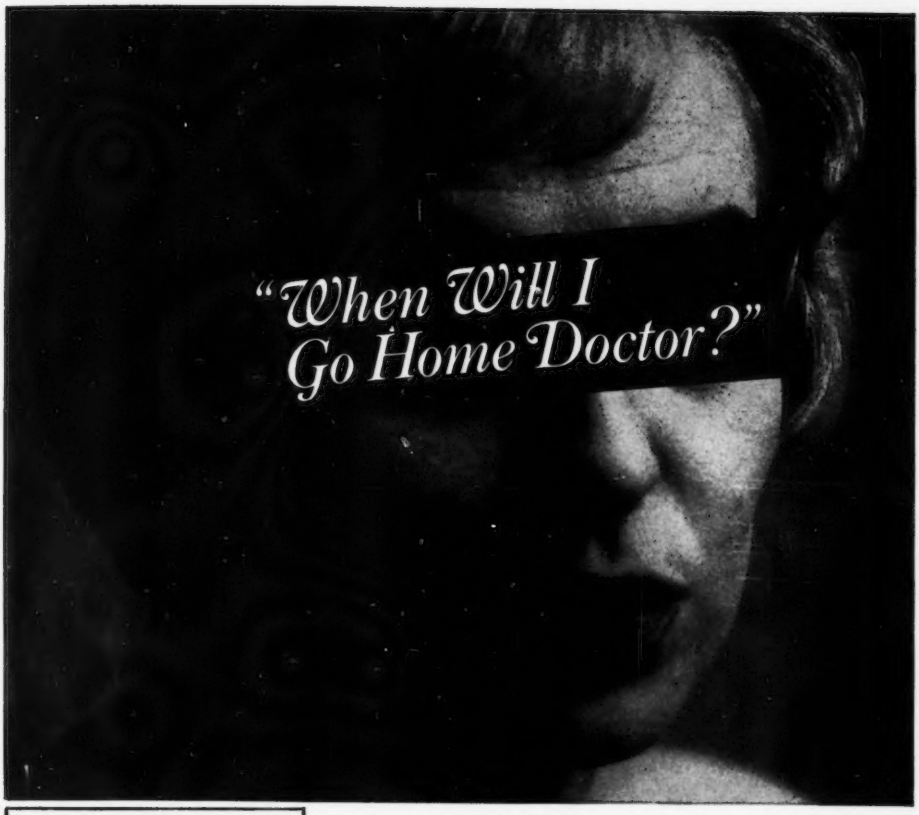

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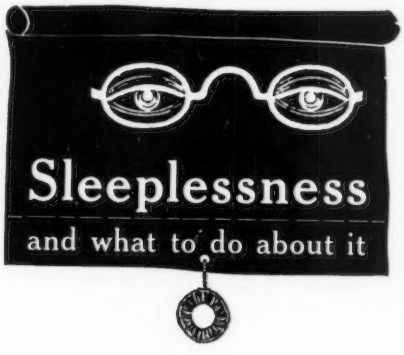

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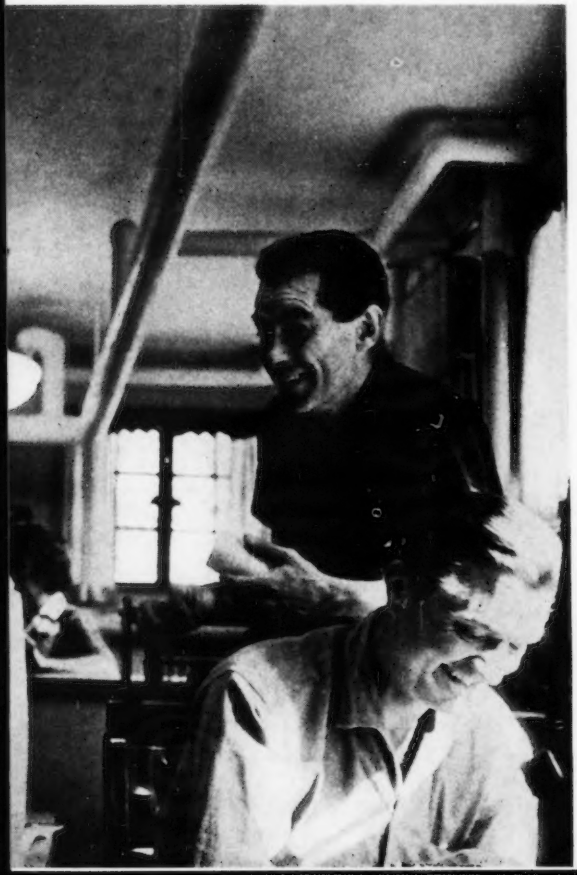

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References: **1.** Sainz, A.: The Phrenopraxic Activity of a Non-noxious Antidepressant, *Ann. New York Acad. Sc.* (in press) 1959. **2.** Thal, N.: Cumulative Index of Antidepressant Medications, *Dis. Nerv. System* 20:197 (May) 1959. **3.** Saunders, J. C.; Roukema, R. W.; Kline, N. S., and Bailey, S. d'A.: Clinical Results with Phenelzine, *Am. J. Psychiat.* (in press) 1959.

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The Cerebral Hemispheres and the Highest Integrative Functions of Man

LORING F. CHAPMAN, Ph.D., and HAROLD G. WOLFF, M.D., New York

Introduction

The relation between brain and mind still awaits clarification despite its long history of evolving concepts and the many distinguished studies concerned with it, notably those beginning in the 18th and extending through the 19th and 20th centuries. Since those who have most to do with the brain as a structure are but rarely the same persons who have the most sustained interest in, and the best insights concerning, man's highest qualities, a dilemma ensues. Physicians concerned with the survival of patients and better methods of localizing lesions and defining disease understandably relegate to second place those evidences of impaired brain function not leading to the furtherance of their professional purposes. Yet these very manifestations are central to the problem of human brain function. They thus remain largely unstudied by both physicians and scholars.

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Recorded for publication June 29, 1959.

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From the Study Program in Human Health and the Ecology of Man and the Departments of Medicine (Neurology) and Psychiatry, the New York Hospital-Cornell Medical Center.

jects for study. It is, therefore, not surprising that the author of the earliest known document concerned with the consequences of wounds of the head probably served as a military surgeon. The Edwin Smith Egyptian Surgical Papyrus [1] (a copy made in 1700 B.C. of a manuscript composed about 3500 B.C.) describes typical patients with wounds in the head as they epitomized general principles. In this remarkable document a specific word for the brain first appears. The observations of the author reveal that he was familiar with many of the features of the consequences of brain injury, including loss of movement of the limbs and eyes and impairment of speech capacity. He even appears to have been alert to the possibility that the site of damage within the brain shaped the symptomatology presented. For example, Case 8 describes a patient with a compound-comminuted skull fracture: "Shouldst thou find that there is a swelling protruding on the outside of that smash which is in his skull, while his eye is askew because of it, on the side of him having that injury which is in his skull, and he walks shuffling with his sole on the side of him having that injury which is in his skull. . . ." The author's failure to assign the motor defects to the opposite hemisphere might conceivably have stemmed from observations of persons with contrecoup injuries. Nevertheless, it indicates a concern with the site of damage within the head as it influences motor function and thus at this early date introduces the question of localization of functions in the brain.

By contrast, those less familiar with injured or diseased brains were slower in accepting the brain as a leading organ in the functions of the body. Attacking the mind-body paradox from the framework of the ideal, they lacked the opportunities for direct observation and rapid verification available to those confronted with persons suffering head wounds. Accordingly, the highest-level functions, by whatever name, have at various times been assigned to the heart, the liver, the stomach, the bowels, the diaphragm, and even the pyloric valve.[2-4] The low estate to which the brain was relegated in ancient Egypt is shown by the indifferent treatment accorded the brain in embalming procedures, as contrasted with the reverence displayed for the heart and diaphragm, which were considered to be especially linked with the soul.

In ancient China, India, and Tibet, the brain was ignored.[5] Human attributes having to do with the spiritual, with personality, feeling, sensation, and mind, were conceived as being seated mainly in the organs of the chest or abdomen, and more on one side of the body than the other. Considered to be vaporous, these attributes were said to enter the body mainly through the mouth and airways, or with death to leave from the top of the skull, through that portion last to ossify in infancy. Since in Oriental thought the body is considered to be a microscopic image of the universe, the relationship of the soul or mind to the body was not formulated in terms of the participation of various portions of the body. Instead, the body's shape and function were explained only in the broadest terms (i. e., Tao, Yin, and Yang).

Homeric Greece considered mind or consciousness (thymos) to be contained in the diaphragm, and thus associated with breath. Observation of the breath's warmth and moisture led to the belief that it was influenced by the blood, which shares those two properties. A distinction was made between "*thymos*," or consciousness, which acted in everyday life and flew out of the body at death, and "*psyche*," the less well-defined "immortal soul," thought to be found in the head. Confusion of the cerebrospinal fluid with seminal fluid led to the belief that the psyche not only was an element of eternal life in man but also was transmitted to form a new individual in procreation.

Alcmaeon, of Croton, in the fifth century B.C., was the first recorded person to attack the problem of brain function by direct anatomical and physiological studies.

He distinguished between thought and sensation and described the optic nerves, concluding that these structures, which he regarded as hollow canals, transmitted visual "impressions" to the brain.

By the middle of the fifth century B.C. in Greece, it was widely accepted that the soul resided in the head.[6] Plato, Theophrastus, Democrites, and Diogenes all considered the brain to be primary in mental functions. In Plato's thinking, mainly expressed in "Timaeus," man's soul was tripartite: It consisted of an immortal soul, and a mortal soul divided in two. All of the soul was contained in the marrow (or the parenchyma of the central nervous system); the immortal portion, "subserving intellect and reason, as well as sensation and voluntary motion," was located in the "spherical, globular marrow of the cranial cavity," which resembled in shape the earth and the universe.[7] Far below the position of the divine soul were the parts of the mortal soul in the "elongate marrow within the vertebral canal." Even below this, "lowest in the spinal marrow, behind the abdominal and pelvic cavities" was found the baser half of the mortal soul. Plato differentiated between the two by saying that the upper was the seat of passion, love, and courage, and the lower, of "desires, meats, drinks, and other things of which it has needs by reason of its bodily nature." In this ingenious arrangement the emotions were just far enough away from the head not to disturb its function, and yet they were near enough to be controlled by reason. The basest part of the soul was "caged" by the diaphragm, like a wild thing.

Hippocrates'[8] excellent descriptions of the signs and symptoms of disease of the brain made at this time are the more impressive in view of the scarcity of neuroanatomical knowledge at the time. The Hippocratic treatise "On the Sacred Disease" includes the well-known statement "with the brain we think, we reason, and we see and hear, and recognize good and bad, and we rave and become alienated." In another Hippocratic work, "On Injuries of the Head," it was recognized that "if the wound be situated on the left side, the convulsion will seize the right side of the body." By contrast, in the Hippocratic concept, passion and feelings were thought to stem from the heart and diaphragm.

Aristotle,[9,10] in his earlier writings, chose the heart as the seat of the spirit and assigned the brain the function of acting as a cooling agent—albeit a most important function, since it permitted man's superior rank over the less noble animals by allowing the heart to remain cool enough to permit superior mental activity.

"The vital spirit is distributed in the blood throughout the blood vessels to all the organs of the body, vitalizing them. The one great exception to this is the brain, which is bloodless and therefore insensitive and cold." Aristotle went on to say: "The sensations of an animal, in particular man, depend upon the balance of the intensity of heat arising from the heart and the cooling process of the brain. Animals lower or less noble than man have insufficient brain to effect optimal cooling. Man's superior intelligence depends on the fact that his large brain is capable of keeping the heart cool enough to permit optimal mental activity." The brain itself was "insensitive," he said, and "without mental activity." However, the doctrine of the seat of the soul in the heart does not represent Aristotle's final version of the relationship of the mind to the body. His formulations evolved further and further from the Platonic duality of mind and body toward a unitary concept. In "De anima," he ultimately concluded that the soul can have no local residence but is present in each part of the organism.[11]

In Alexandria (350 B.C.) the first known systematic dissections of the human body were performed. Here Herophilus and Erasistratus studied the morphology of the brain, distinguishing the cerebrum from the cerebellum. Also, according to Celsus (A.D. 30)[12] and Tertullian, Herophilus vivisected condemned criminals. Herophilus

gave the first clear description of the ventricles of the brain, although Aristotle and Hippocrates both considered the brain to contain a cavity in its interior.

The major figure in ancient neuroanatomy was Galen, who lived during the height of the Roman Empire, A.D., 130 to 200. Part of Galen's training was acquired in Alexandria, although at that time dissection of the human body no longer was permitted and Galenic anatomy was based chiefly on dissections of the ox, the pig, and the Barbary ape. Influenced by the earlier Alexandrians, Galen accepted the view that the fluids of the brain were the locus of sensation and the place of origin of bodily movement. He held that the "psychic pneuma" is created in a knot of blood vessels at the base of the brain and postulated that the watery fluids contained in the sizable chambers of the brain transmitted "pneuma" to the cord and thence, via the nerves, to the body generally. A valvelike arrangement between the chambers of the brain supposedly regulated the ebb and flow of the fluid, and so influenced sensation and movement.

According to Galen, the "natural spirits" (the products of nutrition) passed from the liver and the gut to the heart and were there modified by the material from the lungs. A portion of the resultant product, known as the "vital spirits," was passed to the head. Here, within the rich collection of blood vessels of the base of the brain, a watery distillate was recovered and mixed with air that supposedly entered the cranial cavity through the porous base of the skull above the nose. The by-products of the process were said to be drained off via the stalk of the pituitary into the nasal cavity.

Galen's studies of the brain were made almost exclusively on the ox brain. Since the specimens were not hardened in preservatives, it is not surprising that his concepts of function involved the flow of fluids, and that he placed great emphasis on the ventricles of the brain, an emphasis that persisted for 2,000 years.

Despite this emphasis, he did not neglect the substance of the brain. In a famous passage of Galen's works (De Placitis[13]), he discussed the concept that the ventricles of the brain might be the seat of the soul, a possibility he rejected in favor of the substance of the brain. He reached this conclusion on the grounds that in man, although wounds that penetrate to the ventricles lead to loss of sensation and motion, survival is possible and the mind not destroyed. He inferred that the loss of ventricular fluid was responsible for only the loss of sensation and motion, and that therefore the dwelling place of the soul must be in the substance of the brain. The Byzantine physician Poseidonius (fourth century A.D.) said that injuries of the anterior part of the brain interfered with sensation, while damage to the posterior portion interfered with memory. He assigned the more ephemeral faculty of reasoning to the central ventricle.[14]

The Christian authors of the fourth century A.D. (Nemesius and St. Augustine),[15,16] in contrast, favored the ventricular fluid over the solid substance of the brain as the dwelling place for the soul and its mental faculties, perhaps on the grounds that the ventricular fluids were more suitable than the substance of the brain as an intermediary between the body and the noncorporeal soul.

The mental faculties were defined and classified in accordance with the classic trilogy, and each was assigned to a cerebral ventricle. These chambers (cellulae) were erroneously described as three in number and lying in a straight line in the midst of the head on an axis between the eyes and the occiput. The faculties were assigned in much the same arrangement as that used by Poseidonius. To the first (anterior) cellula was assigned sensation, fantasy, and imagination; to the second, reasoning, intelligence, and thinking, and to the third, motion, and memory, although the details of this arrangement differed with the early Christian authors of this period.

Many of the early medieval Christian authors followed Plato in subscribing to the location of mental functions in the brain, but the heart was chosen by others. For example, Hildegard of Bingen (1098-1170) considered the heart to be the site of mental functions,[17] not on the basis of Aristotle's views but, rather, in keeping with the biblical tradition, for Aristotle's works were not available to Western scholars until the end of the 12th or the middle of the 13th century, at the time of the Crusades. The Aristotelian view of the heart as the seat of the soul was accepted by Avicenna (980-1037) in the Arabic world and gained wide acceptance in Europe after the 13th century. Even Harvey (1578-1657), who so elegantly demonstrated the nature of the heart's action and the circulation of the blood, and who detected that reflexes involving the nervous system were implicated in sensation and motion, held to the Aristotelian view that the apparatus of feeling is in the heart and blood. Thus, in the Western world throughout at least 2,000 years opposing views were held as to whether the mind is in the heart or in the brain, and, if in the brain, whether in the fluid of its ventricles or in its substance. Further, although concepts of the mind-body relationship were often based on erroneous, even fantastic, hypotheses, and although the physiological explanations changed greatly, the idea persisted that the soul was contained in no one organ.

The Renaissance.—Following Galen, it was a thousand years before knowledge of the anatomy of the brain again advanced. It is interesting that the church authorities in Italy became more liberal in their attitudes toward natural science much earlier than in countries more removed from the Papal seat. Human dissections were performed in the Italian universities as early as A.D. 1200, simultaneously with the beginning of the decline of the mysticism that had superseded the Greco-Roman period. Vesalius was the first major author to limit his descriptions to what he had seen personally rather than to quote Galen, as had been the custom for a millenium. The seventh book of his "Fabrica" (1543) was devoted to the nervous system [18] and corrected many of Galen's errors, including his imperfect description of the cerebral ventricles. Henceforth anatomical knowledge of the brain moved forward without faltering.

Physiology, however, lagged behind anatomy. Vesalius himself said: "How the brain performs its functions in imagination, in reasoning, in thinking, and in memory (or in whatever way, following the dogma of this or that man, you prefer to classify or name the several actions of the chief soul) I can form no opinion whatever. Neither do I think that anything more will be found out by anatomy." He went on, however, to make a prescient comment: "It were a better view that intelligence depends on a good tempering (*temperies*) of the substance of the brain than on the variation in the structure (*composito*)." Thus, although knowledge of the anatomy of the brain grew rapidly between A.D. 1600 and 1800 (Willis, Vieussens, Ruysch, Valsalva, Vicq d'Azyr, Soemmerring, Reil), study of the physiology of the nervous system remained largely dormant until the early 19th century. Nevertheless, formulations of the functions of the various regions of the brain began to appear during the 17th and 18th centuries (Descartes, Willis, Swedenborg, Whytt). In retrospect, the lack of a concept of the electrical nature of the nerve impulse appears to have been a severe handicap to these early formulations; and, despite some piercing insights, the gulf between structure and function at that time was still so wide as to require inductive leaps of such length as to remove these early inferences for the most part from scientific value.

Descartes,[11,19] in the early 17th century, elaborated the Galenic concept of the functions of the nervous system, preserving the hydraulic model of fluids flowing through tubular nerves. Although primarily a philosopher, he gave his attention to the anatomy of the brain in the hope that in this way knowledge of the soul might be

achieved directly by observations of its dwelling place and the manner of its transduction into bodily phenomena. This reasoning, although attractive at a time when many philosophic problems were yielding to direct recourse to nature, was dangerously close to heresy. Descartes fashioned a grand compromise. Matter and mind, he stated, although essentially independent and not capable of affecting one another, exhibited such a close "parallelism" that they gave the appearance of being related—thus study of one was relevant to the study of the other without necessarily accepting heretical "materialistic" theories. In keeping with theological orthodoxy, he viewed the brain as an instrument rather than as a generator of mental life. However, in his famous treatment of the pineal body, Descartes took a step closer to open conflict with the church. He elevated this insignificant protrusion within the chambers of the brain to the position of the "seat of the soul," a function to which it appeared ideally suited because of its central position within the brain, its intimate relationship with the fluids of the ventricles, and of the unity of its apparently unpaired morphology, an important quality, since a "sensory commune" bilaterally represented would necessarily imply dual sensation. To quote:

> The soul is really joined to the whole body, and we cannot, properly speaking, say that it is in any one of its parts to the exclusion of the others—the body being unitary, i. e., in some fashion indivisible, in virtue of the disposition of its organs, which are so related each to the others, that when any one of them is removed, the whole body is rendered defective. Again, the soul is of such a nature that it has no relation to extension, nor to the dimensions or other properties of the matter composing the body, but only to the whole assemblage of its organs, as appears from our inability to think of the half or the third of a soul, or of its occupying a space. It does not become smaller on the removal of a part of the body. When, however, the assemblage of the bodily organs disintegrates, it itself, in its entirety, withdraws from the body.

And again according to Descartes:

> There is a small gland in the brain in which the soul exercises its function more specifically than in its other parts. We have also to bear in mind that although the soul is joined to the whole body, there is yet in the body a certain part in which it exercises its functions more specifically than in all the others. It is a matter of common belief that this part is the brain, or possibly the heart—the brain because of its relation to the senses, the heart because it is there we feel the passions. But on carefully examining the matter I seem to find evidence that the part of the body in which the soul exercises its functions immediately is in no wise the heart, nor the brain as a whole, but solely in the innermost part of the brain, viz., a certain very small gland, situated in a midway position, and suspended over the passage by which the animal spirits of the anterior cavities communicate with those of the posterior cavities, in such fashion that its slightest movements can greatly alter the course of these spirits and reciprocally that any change, however slight, taking place in the course of the spirits can greatly change the movements of this gland.[19]

Swedenborg[20-22] (De Cerebro, 1741-1743) specifically refuted the hypothesis that the pineal body is connected with higher-level functions and argued on anatomical grounds that the cerebral cortex was the seat of these functions:

> Neither the cerebellum nor the cerebrum communicate its action to this gland [pineal]. It is from its surface where is conglomerated its cortical substance, that is to say, the origin of its fibers, that the cerebrum acts, and not from its center. Nay, it does not determine a single fiber towards the center, but brings it forth by other paths entirely. So likewise the cerebellum. This gland, therefore, is the center of the actions of the cerebrum, cerebellum, and medulla oblongata only in respect to their chemical functions but not in respect to their sensations and motions.[20]

Swedenborg was avid for knowledge of how the brain performed its work. His "Inductions" concerning the functional significance of the various anatomical structures of the brain included early statements of localization of functions in the cortex:

> The muscles and actions in the ultimates of the body depend more immediately upon the highest parts; upon the middle lobe, the muscles that belong to the abdomen and thorax, and upon the third lobe, those which belong to the face and the head. . . . If this [anterior] region of the cerebrum is wounded, then the interior senses—imagination, memory, thought—suffer; the very will is weakened and the power of determination blunted. . . . This is not the case if injury is in the back of the cerebrum.[22]

As it became possible to discern the course of nerves, and of pathways within the

central nervous system, formulations of the relationship of the anatomy of the solid portion of the brain to functions began to be made. Much interest was centered on the search for a site in the head where all sensation was focused, the so-called *sensorium commune* at first assumed to be in the most anterior portion of the three-ventricle system. The most commonly accepted site for the "sensorium commune" during the late 18th and early 19th centuries was in the brain stem.[23,24] It had been recognized that the medulla oblongata was a region of convergence of pathways from the spinal cord, as well as the cranial nerves. Prochaska, in 1784, stated:

> It certainly does not appear that the whole of the cerebrum and cerebellum enters into the constitution of the sensorium commune, which portions of the nervous system seem rather to be the instruments that the soul directly uses for performing its own actions, termed animal; but the sensorium commune, properly so called, seems not improbably to extend through the medulla oblongata, the crura of the cerebrum and cerebellum, also parts of the thalami optici, and the whole of the medulla spinalis; in short, it is coextensive with the origin of the nerves.[25]

In contrast with the growing interest in the solid parts of the brain, Soemmerring (1796) perserved the medieval tradition by maintaining that the fluids of the cerebral ventricles are the "seat of the soul."[26] Kant and Goethe independently replied to Soemmerring by denying the logic of restricting the soul to only a portion of the body. In one of Kant's letters to Soemmerring on the subject, he separates the mind-brain problem into soluble and insoluble parts. The soluble part of the problem, he stated, is limited to discovering correlations of motion and sensation with the brain, "these alone admitting of a spatial relationship within the brain."

During the 19th century interest in the brain stem as the seat of highest-level functions waned in favor of the cortex. By 1853 Carpenter[27] had moved the seat of consciousness from the medulla forward into the thalamus, and also accepted a contribution of the cerebral cortex to highest-level functions:

> The sensory ganglia constitute the seat of consciousness not merely for impressions on the organ of sense, but also for changes in the cortical substance of the cerebrum so that until the latter have reacted downwards upon the sensorium we have no consciousness either of the formation of ideas, or of any intellectual process of which these may be the subjects.

After 1870 the concept of *sensorium commune* was abandoned, and by the end of the 19th century the cerebral cortex was widely accepted as the seat of "the intellectual functions, intelligent sensation or consciousness, ideation, volition and memory."[28]

The Beginnings of Cortical Physiology

The anatomist Gall opened the era of modern cortical physiology with an error—by reasoning far beyond his evidence. In 1802 he made an elaborate and decisive statement of the relationship of the tissues of the cerebral cortex to "mental" functions, conceiving the cortex to be an aggregate of 27 separate organs, each responsible for a separate mental function, ranging from "language" and "calculation" to "hope" and "philoprogenitiveness." Gall's doctrine conflicted with the theological views of his day by presenting bodily organs as engendering the mind. This heresy was compounded by his division of the "unity of the soul" and led to his expulsion from Austria. Although Gall's concepts were extravagant and gave birth to the pseudoscience of phrenology, he made a lasting contribution by his insistence that the rind of the brain is not inert but does function, especially in thinking and complex behavior. Further, he made a vigorous and well-defined statement of a hypothesis of regional localization of function in the cerebral hemispheres.[29,30]

Gall's statement led to a lively controversy. Outstanding among those who challenged his position was the biologist Flourens, who conducted experiments in which he contrasted the behavior of laboratory animals before and after he had damaged portions of their brains by surgical ablations or injection of noxious substances.

Flourens was impressed by the relatively few alterations in behavior that followed damage to portions of the cerebral hemispheres. He reasoned from the lack of striking defects, as did many later champions of the holistic doctrine of the functions of the brain that the various local regions extirpated by him could not have been the exclusive locus for specific behavioral functions:

> In effect, not only do all of the perceptions, volitions, and intellectual faculties reside exclusively in that organ, but all of these faculties occupy the same place. If one of these is impaired because of damage to a so-called area of the brain, all are impaired; if one is restored by the recovery of that area, all return. Essentially, the faculties of perception and volition constitute a unitary faculty, and that faculty is located in a single organ.[31]

The "Golden Age" of Cortical Physiology

The views of Gall, on the one hand, and of Flourens, on the other, define the broad outlines of a dispute that continues to the present. During the middle part of the 19th century, many experimental biologists defended the holistic view of the cerebrum, whereas physicians dealing with brain-injured patients were more inclined to accept the hypothesis that in various portions of the cerebrum was the neural equipment of special functions. Dax,[32] in 1836, published his observations that the overwhelming proportion of patients with speech defects following injury to the brain exhibited lesions in the left cerebral hemisphere. Also, many clinicians (Bouillaud) accepted Gall's statement that speech defects were associated with frontal lobe injury. These two localizing concepts were combined by Broca.[33] While under his care, a patient who for 30 years had been unable to speak died after a gangrenous infection. Examining the brain, Broca found that, although lesions were found in other lobes also, the only portion of the left frontal lobe that appeared diseased was the area at the base of the third frontal convolution. Here, he localized the "center" for speech. Shortly thereafter, Fritsch and Hitzig[34] (1870) demonstrated that body movements could be elicited by electrical stimulation of some portions of the cerebrum but not by others, confirming the prediction of Jackson (1864), based on observations of patients with focal epilepsy, that an area governing isolated movements existed in the cerebral cortex.[35] Hitzig[36] (1874) also showed that ablation of the prefrontal areas of dogs did not lead to motor disturbance, whereas ablations placed more posteriorly did.

The observations of Broca and Fritsch and Hitzig firmly established the principle that, at least in regard to some of the behavioral functions, the cerebral hemispheres are not functionally equivalent throughout their extent. Further definition of the "motor area" was achieved by the studies of Ferrier[37] (1876), Beevor and Horsley[38] (1890), and Sherrington (1901-1903) and his students.[39]

Regions specifically related to sensations also became clearly defined at this time. Ferrier[37] (1876), Munk[40] (1880), and Beevor and Jackson[41] (1890) related the hippocampal region to olfaction.

Although the auditory radiations were traced to the temporal lobe by Heschl in 1878,[42] no clear statement of the changes in auditory function that follow ablation of the "auditory cortex" could be made.

Flourens[43] (1823) had observed visual defects following cerebral ablations in laboratory animals, and Panizza[44] (1855), after examining the brains of patients who had exhibited visual defects following strokes, concluded that the parieto-occipital cortex was essential for vision. Hitzig[36] (1874) demonstrated that dogs exhibited visual defects following damage to the posterior portion of the cerebral hemispheres alone. The nature of the defects and the extent of the "visual cortex" were further explored by Ferrier[37] (1876), Munk[40] (1890), and Schäfer[45] (1890), leading to restriction of the "visual cortex" to the area striata by Minkowski[46] (1911), Holmes[47] (1918), and Poliak[48] (1933). Klüver[49] exhaustively defined the nature and range

of visual defects following damage to the visual cortex (1933).

Somatic sensation was related to the posterior cortex by Jackson[50] (1887) on the basis of observations of patients with focal epilepsy, but the extent of the sensory cortex and the nature of the defects produced by damage to these areas became the subject of a lively controversy between the English and the Continental schools between 1880 and 1900. Head and Holmes[51] (1911) did much to establish the nature of the defects produced.

These observations on the relationship between the cerebral cortex and sensory and motor functions gave fresh encouragement to those who argued for regional localization of the highest-level functions. The frontal lobe, perhaps because of its apparent position at the apex of the neuraxis, and perhaps in part because of man's large forehead, had been selected early as the seat of intellectual faculties. Gall specified the lobe to contain most of the faculties that could be called intellectual.

Cuvier[52] (1810) believed the entire brain to be concerned with highest-level functions, but he implicated the frontal lobes especially in such functions by pointing out that the frontal part of the head is particularly enlarged in man as compared with lower animals. Gratiolet[53] (1854) interpreted this enlargement as indicating that the frontal lobes are especially concerned with thought and complex functions. (Weidenreich[54] in 1946, argued that the parietotemporal cortex has enlarged proportionally as much as the frontal lobes.)

The concept that the frontal lobe is particularly concerned with high-level functions was also furthered by Bigelow's (1850) report of profound changes in personality of Phineas Gage, a railroad worker, following an explosion in which an iron bar passed completely through the skull, piercing the frontal part of the brain.[55]

Ferrier, combining experimental ablation studies on laboratory animals with a busy practice in a neurological clinic, expanded Hitzig's observations on motor responses to electrical stimulation of the cerebral cortex. He sought to integrate the widely accepted view that the frontal lobes were especially concerned with the highest-level functions and the holistic view that the highest-level functions could not be "localized" in limited regions of the brain. He attempted to do this through the concept that motor centers are "localized" in the cerebral cortex. He observed that centers for movements of the head and eyes could be demonstrated in the frontal lobes—since these movements are an essential component of attention, the frontal lobes are, therefore, particularly related to attention and related faculties.

Ferrier concluded:

> We have, therefore, many grounds for believing that the frontal lobes, the cortical centers for the head and ocular movements with their associated sensory centers, form the substrata of those psychical processes which lie at the foundation of the higher intellectual operations. It would, however, be absurd to speak of a special seat of intelligence or intellect in the brain. Intelligence and will have no local habitation distinct from the sensory and motor substrata of the cortex generally. There are centers for special forms of sensation and ideation, and centers for special motor activities and acquisitions, in response to and in association with the activity of sensory centers; and these in their respective cohesions, actions, and interactions form the substrata of mental operations in all their aspects and all their range.
>
> We have not yet found, nor are we likely to discover, any simple formula to express the relation between brain and mind. It is not a mere matter of brute weight or quantity, absolute or relative; though there is no doubt that in animals of the same order a brain below a certain standard of weight is incompatible with normal intelligence.

Other experimentalists continued to deny a special contribution by the frontal lobes to the highest integrative functions. Outstanding among these were Goltz, Munk, and Loeb. Goltz[56] denied that the highest-level functions could be localized to any region of the brain. He emphasized that there is a direct relation between the extent of the brain lesion and the severity of the behavioral defect:

> We can now reaffirm that every severe injury to both cerebral hemispheres impairs the intelligence of animals to a high degree; idiocy is produced. Flourens' principle that intelligence is not im-

paired following partial removal of the cerebrum is only partially correct. To be sure, in many cases following removal of tissue from the cortex of one hemisphere, intelligence is not perceptibly encroached upon. However, as both hemispheres are reduced in mass, distinct and lasting impairment becomes predictably present. In general, it can be stated that the degree of idiocy following damage to the cerebral hemispheres follows in equal degree the spatial extent of the injury.[56]

Goltz reported that posterior ablations in dogs produced a greater degree of dementia than did anterior removals, an observation he interpreted as stemming from the greater mass of tissue in the posterior quadrants. Munk also observed that lesions of the occipital lobes resulted in the greatest impairment. He, too, supported the holistic hypothesis of the highest-level functions and postulated that, whereas areas concerned with vision, audition, and touch are localized in various regions and are bound together by rich interconnections, it is the aggregate functioning of these sensory fields that is responsible for psychic functioning. (Munk reported "mind-deafness" as resulting from bilateral extirpation of the temporal lobes in the dog, and Ferrier limited the critical region for audition to the superior convolution. These findings of Munk, Goltz, and Ferrier prompted Burckhardt[57] [1890], a Swiss psychiatrist, to attempt to relieve psychotic patients of their auditory hallucinations by removing the cerebral tissue comprising what in his conception was the auditory projection area from four patients. In vague terms he reported satisfactory outcome in three of these and death in the fourth.)

Contemporaneously with Ferrier's works, Jackson's observations on patients with epilepsy led to his formulation (1890) that the prefrontal lobes, as the site of the "highest motor centers," along with the "highest sensory centers" in the posterior portion of the cerebral hemispheres, made up the "physical basis" for mental functions. Hitzig, meanwhile, continued his experiments with ablation of various portions of the cerebrum of a variety of laboratory animals, including monkeys. He maintained his belief that the frontal lobes were particularly concerned with highest-level functions:

I find myself in opposition to Munk as regards the higher intellectual functions and their relations with the anatomical substratum. Munk holds that there are no such things as special organs for these functions and there is no necessity for them. I believe with him that intelligence, or, more correctly, the store of ideas, is to be sought in all parts of the cortex, or, rather, in all parts of the brain, but I hold that abstract thought must of necessity require particualr organs, and those I find in the frontal brain.[30]

Anatomical support for the concept of special centers for highest-level functions was furnished by Flechsig's (1896) study of the temporal order, in which the white matter of the cerebrum becomes myelinated after birth.[58] He concluded that the cortex was divisible into "projection" (motor and sensory) areas, which become myelinated early, and association areas, which do not become myelinated until later. He also inferred that the large parietotemporo-occipital area was of greater importance for mental life than were the frontal association areas.

Loeb[59] (1900) challenged this division, again reasoning from the lack of striking defects observed after cerebral ablations in dogs.

Hitzig and others assumed that the frontal lobes of the cerebral hemispheres are the organs of attention. I have repeatedly removed both frontal lobes in dogs. It was impossible to notice the slightest difference in the mental functions of the dog. . . . Flechsig thinks that it is not only the frontal lobe but the cortex of certain other regions which is responsible for mental activity, inasmuch as it is the seat of "centers of association." I have removed the cortex of Flechsig's "centers of association" in dogs without having noticed anything that justified Flechsig's hypothesis.

Loeb concluded that "associative processes occur everywhere in the hemispheres and possibly in other parts of the brain."

Cortical histology progressed rapidly at this time (Campbell[60] [1905], Smith[61] [1907], and Brodman[62] [1909]). This division was carried to extremes by the Vogts[63] (1919), who reported more than 100 different "areas" in the human brain. The number of distinct histological areas was

reduced by von Economo and Koskinas[64] (1925) and eventually redefined in a relatively uncomplicated manner by Bailey and von Bonin in the 1940's.[65,66]

Von Monakow[67] (1914), studying dogs and monkeys after cerebral ablations, supported Munk in the controversy over localization of functions in the cortex. Whereas Munk interpreted the higher-level functions as stemming from the manifold connections linking the various sensory fields, von Monakow emphasized that the coordination of motor areas also was implicated. In the United States, Franz[68] (1907) improved the methods available for demonstrating defects in behavioral capacity by training animals to perform tasks before injuring their brains, then assessing their capacity to perform these tasks after the injury, and to relearn them if they had been lost. Employing relatively small lesions, he reported that injury to the frontal lobes destroyed recently formed habits, leaving long-standing habits unaffected. However, animals that had thus lost these habits could relearn them in as few trials as originally were required. He concluded (1907): "The loss of functions of intelligence depends not upon a given point in the cerebral lobes, but upon the degree of general alteration of the lobes."

Meanwhile, observations on patients who survived injuries to the cerebral cortex continued to accumulate. Bigelow's (1850) description of Phineas Gage, the "iron-bar" accident victim, was expanded to a complete report by Harlow[69] in 1868. Gage exhibited profound alterations in his behavior, changing from an intelligent, hard-working, and responsible person into one who was "irreverent, profane, impatient of restraint; obstinate, yet capricious and vacillating." He became less concerned for the welfare of his family and refused to return to his work. Harlow's report, appearing at a period of active investigation of the functions of the cerebrum, did much to establish the "syndrome" of behavioral features characteristic of those with frontal lobe injuries. This description was supported by Mendenhall[70] (1869), who described a patient in whom an ax wound had damaged the brain "above the ear." The patient changed from being "quiet, unassuming, rather stupid and honest" to being "noisy, self-sufficient, sharp, and seemingly devoid of moral sense or honesty." Starr[71] (1884) collected a series of 50 patients with brain damage, concluding "that the processes involved in judgement and reason have as their physical basis the frontal lobes."

During the years between 1880 and the beginning of World War I, the concept of a "frontal lobe syndrome" appearing in persons with damage to the frontal lobes was further defined and expanded to include such features as elation, volubility, improper language, apathy, carelessness in dress and personal grooming, "confusion," feelings of fatigue, lack of interest, physical weakness, "childishness," *Witzelsucht*, euphoria, "moral insanity," ready weeping, loss of "shame," difficulty in maintaining attention, lack of initiative, and deterioration in logical thinking (Welt,[72] Jastrowitz,[73] Pick,[74] Müller,[75] Schuster,[76] Elder and Miles,[77] Pfeiffer[78]).

New Data from World War I.—Following this period of active experimental investigation of the functions of the cerebral hemispheres, mainly on laboratory animals, World War I produced large numbers of patients with head injuries on whom the newly formed concepts could be tested and expanded. Roper[79] (1917), Forster[80] (1919), and Marie[81] (1919) expanded the description of the symptomatology of cerebral injuries (linking these symptoms particularly to the frontal lobe) to include loss of spontaneity, loss of memory, lessened emotional response, poor judgment, "moral defects," bulemia, apathy, laziness, difficulty in learning, lassitude, slowness in thought and movement, and increased irritability. Feuchtwanger[82] studied more than 400 patients with brain injuries. In addition to noting many of the features listed above, he found that laboratory testing demon-

strated only slight defects. Those changes that were observed could not be related to the side of head injury or to the anterior-posterior axis of the brain. In contrast with the paucity of "intellectual" defects observed, he reported predictable changes in emotion and volition, which he related especially to the frontal lobes. Goldstein and Gelb [83] (1918), by contrast, did report defects in "intelligence" in a similar group of patients, particularly in those with left frontal injuries. They reported that subjects with frontal lobe damage had difficulty in synthesizing complex stimuli into meaningful perceptions. Later (1939) Goldstein [84] wrote that the syndrome of defects characteristic of those with frontal lobe injury stemmed from a basic disturbance of the ability to deal with abstract concepts and the concomitant adoption by these patients of a "concrete" attitude. Kleist [85] (1934) described his observations on over 300 brain-injured patients. They exhibited many of the features of the "frontal lobe syndrome," which Kleist separated into intellectual defects (associated with the lateral surfaces of the frontal lobes) and defects in the expressions of affect (associated with the orbital surfaces), a localization confirmed by Grünthal [86] (1936) and preserved by Nielsen [87] (1936) and by Fulton [88] (1951).

World War I was followed by an increased number of reports of the behavioral changes associated with brain tumors. Browning [89] (1921), Baruk [90] (1925), Purvis-Stewart [91] (1929), Martin [92] (1928), and Holmes [93] (1931) described changes in highest-level functions observed in patients with brain tumors. These included moral deterioration, naïveté, confusion, irritability, loss of initiative, absentmindedness, forgetfulness, "dulling" of mental activity, increased reliance on others, apathy, and defective attention. These changes were reported to occur most frequently in patients with tumors of the frontal lobe. Gibbs (1932) [94] analyzed the relative frequency of occurrence of symptoms in 1,545 patients with tumors in various regions of the cerebrum. Frazier reported 105 patients with frontal lobe tumors in 1936,[95] and in 1953 Strobos [96] summarized the symptoms present in 898 patients with temporal lobe tumors.

The period following World War I also began a renewed attack on cerebral physiology by means of ablation experiments on laboratory animals. Lashley introduced important new methods.[97] Bianchi [98] (1923) published his results of experiments, going back to 1883, in which he had ablated portions of the cerebral hemispheres from a wide variety of laboratory animals. He stated that "unilateral destruction of the prefrontal lobe of the dog was not followed by any noteworthy symptom, while bilateral destruction brought into evidence a distinct alteration of character, marked especially by weakening of all the highest level manifestations: defects in judgment, exaggerated fear, amnesia, defects in perception, defects in initiative and resource, impaired capacity to perform complex movements, and diminished vivacity." He was careful to express his opinion that the entire brain contributes to intellectual functions, but stated that his "hypothesis is that the frontal lobes are the seat of coordination and fusion of the incoming and outgoing products of the several sensory and motor areas of the cortex." He described the highest-level functions thus: "The faculty of utilizing the mental products of the sensory areas of the cortex for the construction of mental syntheses more suited for abstraction, and hence, the cognition of nature . . . which renders possible the unfolding of a long process of logically connected thought . . . giving rise to reactions which on the basis of collective and individual experience permit a higher adaptation of the individual to his physical and social environment." [98]

Contemporary Studies.—Pavlov and his school, in their studies [99-101] of conditioned reactions, contributed the 20th century's most important concepts and experimental methods for studying the highest-level functions of the nervous system. Pavlov's ex-

periments were made initially on laboratory animals and were subsequently carried out in man. He formulated and elaborately demonstrated the principle that heretofore-inconsequential stimuli could assume significance when linked in time with biologically important events. He thus defined the place of signals and symbols in goal-achieving activities. He inferred that the effects of stimulation in the periphery were distributed diffusely in the cerebral hemispheres in spreading waves of excitation and inhibition, implying that any given response implicated much of the cerebral hemispheres. Although systematic studies of the effects of removal of progressively larger portions of the cerebral hemispheres were not made by this school, it was observed that after ablation of major portions of the cerebral hemispheres dogs lost much of their ability to respond differentially to different tones, even though simple conditioned reactions to sound could still be established. It was shown that with more elaborate neural equipment, more and finer discriminations could be made by dogs, and in such animals more complicated chain reactions could be developed. Pavlov concluded that stability or lack of it in maintaining predictable reactions under duress and the capacity to reorganize promptly thereafter were dependent upon some inborn or early acquired capacity.

The effects of the size and location of lesions within the cerebral hemispheres on the ability to solve maze problems were examined in an extensive series of elegantly designed experiments by Lashley [97] (1929). He observed close correlation (coefficients of from 0.57 to 0.80) between the numbers of errors made by rats in running mazes and the extent of the lesions, regardless of their site within the cerebral hemispheres, thus establishing the principle of mass action, at least for the rodent brain.

Richter and Hines [102] (1937) demonstrated a readily observable difference in the behavior of monkeys with frontal lobe ablations as compared with occipital lobe ablations. After bilateral frontal lobe damage they observed a large increase in their spontaneous movements, whereas animals with occipital ablations exhibited a decrease in movement. Jacobsen [103] (1936) reported that chimpanzees with bilateral frontal lobe ablations are impaired in their capacity to solve "delayed reaction" problems. In this procedure food is placed under one of two cups while the animal watches. A screen is lowered for a brief period and then lifted, allowing the animal to select one of the cups to get the food. Jacobsen interpreted defective performance on the delayed response task as indicating a disturbance of recent memory. "Adaptation is inadequate in those situations which require for their solution not only present sensory items but also elements of past experience." The response of these animals when they failed to select the appropriate cup changed from enraged shrieking and aggressive behavior to a calm equanimity after removal of tissue from the frontal lobes. These changes were reported in 1935 to the International Neurological Congress, prompting Egas Moniz to suggest surgical damage to the frontal lobes as therapy in prolonged severe disturbances of mood, thought, and behavior in man.

The introduction of ether (1846) and chloroform (1848) as anesthetic agents and the development of the antiseptic method (1867) allowed the rapid development of neurosurgery during the late 19th century, at a time when the facts of cerebral physiology were also rapidly accumulating. Macewen [104] (1881), Durante [105] (1887), Keen [106] (1888), and von Bergmann [107] (1889) reported successful removals of cerebral tumors. Under the guidance of Horsley and Cushing, neurosurgery advanced greatly in the early 20th century, resulting in the preservation of life and the long survival of persons with surgical loss of cerebral hemisphere tissue that could be specified as to location and extent with at least a degree of precision. In 1928, Dandy [108] described five patients in whom one hemisphere had been removed during treatment of cerebral tumors. He reported

that these procedures had resulted in no obvious changes in the highest-level functions. O'Brien [109] (1932) and Jefferson [110] (1937) also reported little or no change in these functions following extensive cerebral resections. Bailey [111] (1933), on the other hand, reported that frontal lobectomy in his experience predictably resulted in changes of character and defects in judgment. Penfield and Evans [112] (1932) reported that they could observe no change in intellectual functioning as measured by laboratory testing procedures following unilateral frontal lobectomies, but they concluded that in the daily lives of these patients they observed an "impairment of those mental processes which are prerequisite to planned initiative." Simultaneously, Brickner [113] presented a detailed account of the daily life of a patient in whom both prefrontal regions had been ablated. The author observed many changes in the highest-level functions of this patient but emphasized that they represented quantitative, but not qualitative, changes. He concluded: "The frontal lobes are not intellectual centers in any sense except perhaps a quantitative one and they play no specialized role in intellectual function."

Ackerly [114] also made a detailed study of the changes that had occurred in the daily life of a patient following frontal lobectomy and noted many of the same features described by Brickner. It became apparent, however (Rowe, 1937 [115]; Lidz [116]; Hebb and Penfield, 1940 [117]; Stookey, Scarff, and Teitelbaum,[118] 1941) that many patients following frontal lobectomy were surprisingly free of obvious defects in mental function and the other features of the "frontal lobe syndrome." Hebb [119] reported that the average Stanford-Binet intelligence quotient for 38 cases of cerebral lobectomies was slightly higher (I. Q. 108) than the average for the general intact population (I. Q. 100). Further, it was striking that successful removal of cerebral tumors was often followed by major improvement of the patient's performance in tests of the high-level functions, an observation indicating that diseased tissue might interfere with the functional capacity of neighboring, and even remote, healthy brain tissue.

In 1935 Weisenburg and McBride [120] contrasted the performance of those with dominant hemisphere cerebral lesions with that of subjects with nondominant hemisphere lesions. They found that, whereas the performance of patients with dominant hemisphere lesions was most impaired on tests having to do specifically with speech function, the performance of those with right hemisphere lesions showed the greatest impairment on tests not related specifically to language. Also, they emphasized the great variation in degree of impairment of speech in subjects with lesions of similar site and extent. On the basis of their studies, these authors rejected the point of Goldstein and Scheerer [121] that the impairment of speech function in patients with aphasia invariably is accompanied by widespread impairment of highest-level functions.

Rylander [122] contributed the next major step in defining the defects following cerebral hemisphere ablations in man by carrying out extensive and informative studies on 32 patients long surviving removal of tissue from the frontal lobes, comparing each with an intact subject selected to match the brain-damaged subject. The subjects were examined by means of a large number of quantitative behavioral tests selected to assess components of the highest integrative functions. Rylander also interviewed the patient and a member of his family in regard to changes that had occurred in the patient's mood, attitudes, and behavior. The subjects were divided into large and small groups. It was found that performance of the brain-damaged group on procedures thought to measure abstract thinking was greatly impaired. Those with large lesions exhibited the greatest impairment. It was also found that scores of the brain-damaged groups on the Stanford-Binet Intelligence Test were lower than those of the intact group. On the other hand, no differences between the

two groups were observed for tests designed to measure immediate memory, new learning, and attention. Four years later, Rylander [123] reported on 16 patients with removal of tissue from regions of the cerebral hemispheres other than the frontal lobes. He found that these brain-damaged subjects did not exhibit the striking defects in laboratory procedures requiring abstract reasoning observed in members of the frontal lobe group that had been studied earlier. Yet interviews with the subjects and their families of the second group indicated that those with nonfrontal lobe injuries also exhibited defects. Rylander concluded:

> My two investigations provide conclusive evidence in favor of the view that most of the symptoms exhibited by the patients in the 1939 study, namely, changes in mood, euphoria in particular, disturbance in initiative, restlessness, deterioration of the higher intellectual functions (e. g., abstract thinking, the power of concentration, acts involving judgement) and negative symptoms, such as the pathological enlargement of the appetite, and an abnormal increase in weight, were due to the maiming of the frontal lobes. The memory functions, on the other hand, seem to be dependent on the activity of the whole cortex, as many other observers have already mentioned. The same condition seems to apply for normal fatigability and a normal power of concentration.

It is noteworthy, however, that an important difference between Rylander's frontal and nonfrontal groups was one of the mass of the lesion. Although Rylander states that "the amount of brain excised in the series of patients operated upon for lesions in the parietal, occipital, and temporal lobes was on a par with the extent of the resections made in the operations on the frontal lobes," examination of the drawings of the extent of the lesions and of the weights of the tissue removed reveals that the nonfrontal series included only one or two subjects with lesions equivalent in mass to those in Rylander's "large frontal" group.

The studies of Halstead,[124] published in 1947, were the next major step forward in human cerebral physiology. Halstead selected, devised, and standardized procedures of greater sensitivity to cerebral injury than any previously developed. At the time of the publication of "Brain and Intelligence," in 1947, few patients with nonfrontal lesions had been tested with all of the components of the "Halstead Battery," and he concluded that much of the impairment observed was specific to the frontal lobes. A later series, reported in 1958 by Shure and Halstead,[125] included a larger number of subjects with lesions in the nonfrontal regions. In this later study it was concluded that, whereas the frontal lobes are particularly important for "abstraction," defects in biological "intelligence" also follow lesions in nonfrontal regions.

> No specific intellectual process is localized in any cortical area such that a loss of function invariably follows removal of that region. However, the various cortical regions are of decidedly unequal importance for the mediation of various intellectual functions. Patients with frontal lobe excisions perform more poorly on almost all tests; however, this difference is statistically significant only on abstraction (A factor) tests on Halstead's Impairment Index.

The mass of the lesions of the subjects reported by Shure and Halstead was reappraised, and performance reanalyzed by us and will be reported in the section on "Results."

A potentially major contribution to the development of a systematic statement of cerebral function is contained in the concept of "biological intelligence," which Halstead introduced as being more appropriate for the functions of the cerebral hemispheres than were conventional psychometric formulations of intelligence. He postulated four major components of biological intelligence: abstraction, power (closely related to "vigilance"), modality, and a central integrative function closely related to memory. This categorization of the components of biological intelligence was supported by the observation that factor analysis of scores on the Halstead Battery also revealed four major factors as principal determinants of performance. The value of Halstead's four-factor theory of biological intelligence remains largely unexamined to the present time, perhaps in part as a consequence of its association with factor analysis, which

bears an uncertain relationship to such formulations.

In 1951 Anderson [126] studied the performance of subjects with focal lesions in the dominant or nondominant hemisphere on the Wechsler-Bellevue Scale. A base-line score was established for each subject, and the performance on the various subtests contrasted with the person's base-line score. He reported that patients with dominant-hemisphere lesions showed greater loss of verbal abilities than did patients with lesions in the nondominant hemisphere.

In 1952 McFie and Piercy [127] studied the performance of 74 patients with cerebral lesions on Weigle's color-form-sorting test, a procedure requiring the ability to abstract such qualities as shape and color and to shift from one grouping basis to another. They concluded that the subjects with nondominant-hemisphere defects were less impaired than were those with dominant-hemisphere defects. It is worthy of note in this regard that in a series of subjects with hemispheric lesions of unknown extent, those with nondominant-hemisphere lesions may be expected to be large in extent, since the conspicuous speech disturbances of those with even small injuries of the dominant hemisphere will cause them to seek treatment. In a second series of studies [128] these authors studied 58 right-handed subjects with lesions of the cerebral hemispheres, employing a larger group of testing procedures. They concluded that impairment of recent memory and of new learning was closely related to size of defect rather than to locus. They again found that tests involving speech functions were impaired to a greater extent in subjects with lesions in the dominant hemisphere. The possibility of contrasting the degree of impairment of speech function with the degree of impairment in highest integrative functions as an aid in localizing the site of cerebral defects has been elaborately worked out and successfully applied by Reitan.[129]

The results of Teuber, Battersby, and Bender's studies [130,131] on veterans of World War II with penetrating head wounds indicated that those with injuries in the posterior third of the hemispheres showed more impairment on several procedures (Hidden Figures test, a sorting test, a visual test of abstraction capacity, and the Maier string test) than did subjects with lesions in the anterior or central portion of the hemisphere. It is to be noted that these testing procedures would be expected to be sensitive to impairment of visual capacity.

In addition to subjects with partial resections of the cerebral hemispheres performed as treatment of neoplasms, epileptic seizures,[132] and vascular anomalies, another group became available after 1936, those with frontal lobe resections performed as treatment for psychosis, neurosis, or intractable pain. During the period from 1940 to 1955 many studies were made of subjects before and after frontal leukotomy or lobectomy performed for these reasons.[133-137] In general, relatively few predictable changes could be observed, although the over-all conclusion can be drawn that the surgical procedures were followed by greater impairment in highest-level functions than had been present previously. Interpretation of the data from these studies is made especially difficult by the major and ill-defined impairment of highest-level functions already present. This complicating factor was minimal in the patients studied by Tow in 1955.[138] From the study of relatively well-preserved patients mainly with "obsessive-compulsive symptoms," he concluded that "after isolation of the frontal areas it must be concluded that man is reduced to a lower level of activity in various aspects of his intellectual life, without there being an actual dementia as clinically understood."

Thus, by the middle of the 20th century the nature of the impairment following loss of tissue from the cerebral hemispheres was fairly well established as regards speech, motility, and sensation, and, in broad outline, as regards the highest-level functions. But, despite the major contributions of Lashley and of Halstead, a comprehensive,

organized statement of the nature of the highest integrative functions was lacking, and the relationship of impairment of these functions to the mass and site of lesions within the hemisphere was not defined. With this background, the study of long-surviving subjects with loss of known amounts of tissue from the cerebral hemispheres began.

Method and Subjects

Selection of Subjects

From the records of the New York Hospital, subjects from whom portions of the cerebral hemispheres had been removed were selected for study. Those selected met the following criteria: (1) A portion of the cerebral hemispheres had been resected; (2) the extent and site of tissue removed could be specified and did not extend beyond the cortex and underlying white matter of the frontal, temporal, parietal, or occipital lobe; (3) no evidence of progressive disease process was present; i. e., the lesion was static; (4) the subject did not exhibit evidence of significant disease other than the local cerebral defect under study; (5) the ages were between 18 and 60; (6) there was no evidence of diffuse disturbance of cerebral hemispheric dysfunction (epileptic seizures, elevated intracranial pressure); (7) the resections had not been performed for intractable pain, obsessions or compulsions, character or behavior disorders, or psychosis; (8) subjects did not exhibit significant impairment of speech or language or significant defects in motility.

Assay Procedures

A. Extralaboratory Procedures in the Context of the Subjects' Environment

1. Interviews were conducted with the subjects concerning their own appraisal of their behavior patterns before and after loss of hemispheric tissue.

2. An intensive survey of the subjects' behavior was made, including data collected from members of their families, neighbors, friends, and employers concerning the subjects' past and current environmental settings, behavior, attitudes, utterances about ideas, and mood and bodily reactions, as well as over-all (interpersonal, social, and vocational) capacity for adjustment before and after hemispheric tissue loss.

TABLE 1.—*Extralaboratory Criteria for Impairment of Highest Integrative Functions*

1. Reduction of the thresholds for "deprivation" and "frustration"
2. Longer-lasting and severer disorganization after frustration, deprivation, failure, or conflict
3. Reduced or inappropriate affective response
4. Impairment of alertness and vigilance
5. Impaired associative capacity
6. Diminished seeking of the nonadapted state
7. Impairment of initiation
8. Impaired abstraction capacity
9. Impaired capacity to fulfill social, vocational, and interpersonal responsibilities
10. Diminished activity to satisfy appetites and drives
11. Impairment of capacity to maintain defense and compensatory reactions within appropriate limits
12. Impairment of capacity to develop and maintain appropriate and effective defensive and compensatory reactions
13. Reduction of the intensity of action patterns
14. Reduction of the duration of action patterns
15. Impairment in orientation
16. Memory defects
17. Reduced learning ability
18. Impairment of skilled actions and sensory-motor efficiency
19. Impairment of perception of self and self-environment relationship
20. Impairment of perception of the environment

3. Protocols of the above data were prepared and analyzed, allowing the establishment of 20 criteria for rating impairment of function (Table 1).

The subjects were assigned ratings from 1 to 5 for each of these 20 criteria. Each subject was rated in terms of alterations from his premorbid patterns and level of performance.

B. Laboratory Procedures

Standardized and commonly known procedures included the Wechsler-Bellevue Scale, Halstead Battery, Rorschach Ink Blots, Porteus Mazes, Columbia Mental Maturity Scale, and the Hartford Shipley Scale, as well as other newly developed procedures.[138–140] In addition, two other quantitative procedures were devised and standardized during the present investigation by the investigators: a frustration test and a conditioned-reaction procedure implemented by an electronic apparatus using auditory and visual stimuli. The conditioned-reaction procedure also assayed perseveration, extinction; the effects of simultaneous stimulations and extrapolation, and reactions to failure; the frustration test assayed reaction to failure.

On the basis of the data from preliminary studies this group of behavioral assay procedures was reduced to five major aggregates.

1. Conditioning procedures *

* The data of this section were gathered in association with Louis Berlin, M.D. They have been reported separately in summary.[147] The apparatus was designed and constructed in association with Mr. John Michael Manring.

The conditioning procedures were of the instrumental avoidance type. Reenforcement of a conditioned response was derived from the successful execution of the response which led to avoidance of a shock. The subject was seated before a panel from which various tones or lights could be presented. On a table at the base of the panel was mounted a response lever, which the subject could move or allow to remain stationary. An electrode was attached to the wrist of the nonoperating hand, and when the response was the wrong one the subject received a mild shock.

The subjects were instructed as follows: "This lever can be moved in any of four directions. If you move the lever at the right time and in the right direction, and not at any other time, nothing will happen to you; but if you fail to move at the right time or if you move at the wrong time at the wrong place, you will get a shock. Your goal is to avoid getting shocks by moving only at the right time and to the right place." The examiner was then seated at a control panel out of view of the subject. The duration of the presentation of the stimulus, the interval between stimuli, and the sequential arrangement of the stimuli were regulated through the signal control panel. Extraneous environmental stimuli were reduced to a minimum. The duration and sequence of stimulation, the time intervals between stimuli, the response made, and whether or not the subject had received a shock were automatically recorded.

The first step in this conditioning procedure was directed toward effecting a stable conditioned response (CR) to a tone of 635 cps presented for one second at 10-20 intervals. If the subject did not respond appropriately, i. e., by moving the lever to the correct position following the tone, he received a shock two to five seconds later. The criterion for a stable conditioned response to the tone Step 1A was 12 consecutive responses in which the subjects avoided the shock.

After a stable CR had been effected in responses to a 635-cps tone, additional stimuli were presented in conjunction with the tone. These stimuli required the subject to withhold movement of the lever to avoid being shocked. Thus, in Step 1B a colored light was presented in the series requiring the subject to withhold movement of the lever to avoid shock. There then followed, 2.5-10 seconds later, the 635-cps tone requiring movement of the lever as in Step 1A. Tones of 220 cps (Step 1C) and 425 cps (Step 1D), respectively, (which called for no movements) were similarly presented, each in turn followed by the 635-cps tone. The subjects were required in each instance to differentiate between the positive conditioned stimulus, requiring movement of the lever to a correct position, and the negative conditioned stimuli, requiring no movement. In Step 1E all the previous stimuli were presented in varying sequence at intervals of one to five seconds, requiring the subject to discriminate repeatedly between the stimuli.

In Sept. 2A, a 328-cps tone was presented alone, requiring the subject to move the lever to a new position. When this response was stabilized, the subject was required to push the lever in response to the 328-cps tone, but to withhold responses to another series of colored lights (2B, 2C). Then the subject was required to respond differentially to a 328-cps tone when presented in sequence with a 425-cps tone requiring no movement (2D), and when all stimuli in Step 2 were presented (2E).

The subjects were once more exposed to the original positive conditioned stimulus (Step 3A). All positive and negative conditioned stimuli used previously were then presented for a total of 100 stimuli in such a way that the subject experienced a shock with each stimulus regardless of response. The subject was then given an opportunity to reestablish the original positive conditioned response (4A) by again withholding shock when the "correct" responses were made.

Scoring of results. Performance in each of the conditioned procedures was scored on the basis of the number of trials required for the subject to establish a stable response to a given stimulus or sequence of stimuli. Items scored consisted of the number of trials required (1) to establish a simple stable conditioned response and several differential responses by discriminating among various tones and lights; (2) to establish a second and different series of conditioned responses; (3) to extinguish a previously established reflex; (4) to reestablish a response following a period of induced failure, during which each stimulus was arbitrarily accompanied by shock. A summation score for the total conditioning procedure that included all scores obtained in Steps 1, 2, and 3 was also computed.

2. The Halstead Aggregate

Care was taken to duplicate in detail the equipment and to follow precisely the procedures proscribed by Dr. Halstead[124] (Table 2).

3. The Rorschach Ink Blots Aggregate†

Analysis of the subjects' responses departed from traditional methods and emphasized the relationship among a number of qualitative, as well as quantitative, features grouped in 28 configurational categories (Table 3). In Table 4 these criteria have been elaborated and rearranged to correspond to the concept of the highest integrative functions developed in these studies. Each subject was assigned a score ranging from 0 to 3 for each of the 28 categories. A score of 0 indicated the absence of the criteria of impairment. A score of

† The data of this section were gathered in association with William N. Thetford, Ph.D. They have been reported separately in summary,[147] and a more detailed presentation is in preparation.

TABLE 2.—*The Component Procedures of the Halstead Aggregate*

1. Categories
   The procedure required the subject to "abstract" and maintain various organizing principles, such as size, shape, and color, from a series of pictures presented on a screen.
2. Flicker fusion rate
   The basic unit of this procedure is a Type 631-B General Radio Strobotac. Low-level illumination critical flicker frequency (CFF) of the subject is measured in 10 trials, allowing the subject to make the settings himself.
3. Flicker deviation
   The average deviation of the last 5 settings made by the subject with Indicator H.
4. Form board time
   A modification of the Seguin-Goddard Form Board test, in which figures cut in the form of ovals, triangles, stars, etc., are fitted into appropriate grooves in a board. Three timed trials are given first with the dominant hand only, then with the other hand, and finally with both hands. The score is the total time required for all these trials. At no time is the subject permitted to see the board; he works while blindfolded.
5. Form board memory
   After 3 timed trials without vision on the form board, the subject is asked to draw an outline of the board from memory, including the shape of the blocks and their position on the board. The score is the number of shapes out of 10 that were accurately drawn as to shape.
6. Form board localization
   The number of figures out of 10 that were accurately localized in the above drawing of the form board.
7. Rhythm
   Performance on the "Rhythm" test of the Seashore tests of musical ability. The test requires the subject to decide whether two rhythms are the same or different. The test is tape recorded.
8. Speech discrimination
   A speech discrimination test, in which nonsense-syllable variants of the "EE" digraph are played back from a tape recording. The subject is required to select the spoken word from among several words printed on the answer sheet.
9. Tapping rate
   A procedure for determining finger oscillation rate. The score is the average of five 10-second trials in which a mechanical counter is tapped as rapidly as possible with the extended index finger of the dominant hand.
10. Time sense
    An electric clock with a sweep second-hand is started by the subject by depressing a lever; he watches the hand indicate 10 seconds and then releases the lever, stopping the clock. After 10 trials the face of the clock is turned away, and the subject is asked to depress the lever for the same period without watching the clock. The score is based on the deviation of the subject's settings from 10 seconds.
11. The index
    Halstead has established criterion scores for each of the 10 components. For each score that is more impaired than the "criterion" score the subject is assigned one-tenth of a point on the index. Thus, a subject whose scores were poorer than the criterion on each of the 10 components would be assigned an index rating of 1.0.

TABLE 3.—*Categories for Analysis of Rorschach Ink Blot Responses* *

1. Stereotyped thinking (2) †
2. Rigidity (6)
3. Anxiety and insecurity (3)
4. Vagueness of perceptions (1)
5. Defects in analytic-synthetic ability (4)
6. Constriction of mentation (5)
7. Deterioration of mentation (9)
8. Lack of planning capacity (10)
9. Defects in abstraction (8)
10. Affective instability (7)
11. Reduction of affect-laden associations (11)
12. Passivity in mentation (13)
13. Poor control of mentation (12)
14. Slowing of responses (16)
15. Satisfaction with inferior performance (21)
16. Social and affective withdrawal (14)
17. Inability to improve performance with maximum effort (17)
18. Loss of ability for self-appraisal (23)
19. Lack of interest (19)
20. Circumstantiality (22)
21. Fluctuation of quality of responses (18)
22. Apathy and inertia (20)
23. Verbosity and rambling (24)
24. Depression (27)
25. Confused, fluid, disorganized thinking (15)
26. Fatigability (26)
27. Inability to share common social attitudes (25)
28. Bizarre, illogical, or highly personalized perceptions (28)
29. Sum of scores for the 28 criteria

* Scoring Method: Each subject was assigned a score ranging from 0 to 3 for each of the 28 categories. A score of 0 indicated an absence of the features of that category in the subject's responses to the ink blots. A score of 3 indicated maximal impairment; scores of 1 or 2 were assigned to intermediate stages of impairment. An over-all score was calculated by summing the scores of the separate categories.

† The number in parenthesis refers to the rank ordering of the mean scores of the individual criteria for 31 subjects with focal loss of tissue from the cerebral hemispheres. Thus, Category 4 was the most predictable criterion of impairment in this series, and Category 28, the least.

3 in any one category indicated maximal impairment; scores of 1 and 2 were assigned to intermediate degrees.

4. Wechsler-Bellevue Aggregate

The Wechsler-Bellevue Adult Intelligence Scale was administered to the subjects. In addition to scoring in terms of the weighted scores of the various groups, a total impairment score was computed which represented the sum of negative difference between the verbal I. Q. and the performance I. Q.

5. Reaction to failure ‡

A laboratory procedure was designed to study the effect of failure on mentation and behavior. An attempt was made to motivate each subject to do well, and therefore make failure meaningful to him. Subjects were presented with 100 cards on which were four symbols, one of which differed from the other three according to a simple principle. A correct response consisted in identifying the position of the symbol that differed from the other three and making an appropriate selection among four levers separately numbered on a keyboard. Selection of a correct lever was followed

‡ The data of this section were gathered in association with Thomas C. Guthrie, M.D. They have been reported separately in summary.[117,118]

TABLE 4.—*Categories for Analysis of Highest Integrative Functions Using the Rorschach Tests Blots*

1. Impairment of Expression of Needs, Purposes and Goal-Directed Activity		
(*a*)	Lack of interest	
	Listless	(19) *
(*b*)	Apathy and inertia	
	Indifference; dry, monotonous voice, lacking in feeling tone	
	Emphasis upon pure tone with reduced affective association	(22)
	Lack of spontaneity	
(*c*)	Reduction of affect-laden associations	
	Evasive and noncommittal comments	(11)
(*d*)	Low level of energy exhibited in dealing with ink-blot stimuli	
	Low level of effort	(12) (14)
(*e*)	Satisfaction with inferior performance	
	Despite inadequate performance, failure to attempt to improve responses even when encouraged to do so	(15)
(*f*)	Lack of evidence of fantasy	(1)
2. Impairment of Mechanisms for Goal Achievement		
(*a*)	Low-level quantity and quality of responses	(7)
	Few responses — general improverishment of responses	(1) (2) (5)
	Difficulty in eliciting associations	
	Responses limited to perception of details	
	Failure to offer scoreable responses to dominant and conspicuous stimuli	
	Frequent reporting of animal forms	
	Narrow range of kinds of forms reported	
	Delayed response time and slowing in all activities	
	Poor quality of forms	
	Poor organization of perceptions and responses	
	Giving a response which is recognized by the subject as being inappropriate	
	Failure to integrate and organize parts and details into a whole	(7)
(*b*)	Lack of planning capacity	(8)
	Responses lack indication of definite plan or method of approach	
	Loose, rambling, poorly organized, and unpredictable sequence of association	
(*c*)	Defects in ability to make abstractions	
	Inability to analyze and synthesize stimuli and perceptions	(9)
	Frequent reporting of a part of a percept that is commonly seen as a whole	
	Inability to recognize that ink blots are actually such and insistence that these are representative of actual objects	(12)
	Failure to perceive the suggestive or symbolic implications of the form and shape of the ink blot and therefore make overliteral interpretations	
(*d*)	Vagueness of perceptions	
	Inability to define, delimit, or clarify responses	(4)
	Impairment in concentration and alertness, as shown by a general distractibility and irrelevant comments	
	Inability to improve poor performance with maximal effort	(17)
(*f*)	Perseveration	
	Repetitive responses lacking in variation	
	Inability to shift from one response to another	(7)
	Perseveration of the same response to different cards	
	Handling of the cards persistently in the same manner	
3. Impairment in Ability to Initiate, Organize, and Maintain Appropriate Defensive Reactions		
	Evidence of Presence of Defensive Mechanism Only Partially Effective	
(*a*)	Poor modulation of affective expression	(10)
(*b*)	Social withdrawn	
	Withdrawn, self-centered attitudes	(16)
	Shallow affective response, disregard of social expectations	
(*c*)	Excessive blaming, projection, suspiciousness	(18)
(*d*)	Constriction	
	Narrow range of content	(6)
(*e*)	Circumstantiality and perfectionism	
	Overelaboration with minor aspects of the blot	(20)
	Meticulous, overly intent examination of the blot, effort to include all elements of the blot	
(*f*)	Overtalkativeness and introduction of irrelevant topics	(23)
(*g*)	Denial of affective content of perceptions	(11)
(*h*)	Depersonalization	(19) (16)
(*i*)	Reaction formation	(11)
	Evidence of Failure or Inadequacy of Defenses	
(*a*)	Anxiety and insecurity	(3)
	Restlessness, self-depreciation, including distrust of own ability	
	Fear-producing perception	
	Expression of aggression and hostility	
	Responses indicating violence, blood, etc.	

(*b*)	Bizarre, illogical, or highly personalized perceptions	
	Peculiar, morbid, or bizarre associations	(28)
	Confabulation, perception of composite of human and animal forms	
	Illogical associations, non sequitur	
(*c*)	Rejection of common social attitudes	
	Few popular responses (low number of animal responses)	(28)
	Frequent departure from common modes of perception	
(*d*)	Depressive affect	
	Painful compliance with requests by examiner	
	Frequent reference to death, disease, and other morbid topics	(24)
4. Impairment of Capacity to Maintain Organization During Stress and to Recover Promptly from Its Effects		
(*a*)	Impaired frustration threshold and tolerance (irritability) and delayed recovery — disorganization	(7)
(*b*)	Responses and behavior during the procedure poorly controlled	(13)
(*c*)	"Blocking"	
	Catastrophic reaction	(10)
(*d*)	Weeping	
	Expression of anger, hopelessness, and inadequacy, and feelings of perplexity	(10)
(*e*)	Labile and unpredictable affective reactions	(10)
(*f*)	Fluctuation in quality of response	
	Variability in form, quality, and organization	(21)
	General fluctuation in initial reaction time and in time spent with each blot (poor answers to every card)	
	Failure to give even popular response on card	
(*g*)	Fatigability	
	Lack of persistence, giving up readily, irritability	(26)
(*h*)	Disorganization of effort and response	
	Disorganized in reporting the perceptions	(25)
	Combination of inappropriate and inconsequential aspects of the blot	

* The number in parenthesis refers to the categories listed in Table 3.

by a pleasant chime sound. An incorrect answer was followed by a loud, disagreeable buzzer sound. After 15 correct responses, the lever box was set so that almost all lever selections evoked the buzzer sound. During a series of 85 induced failures, each subject was observed for lip, mouth, eye, jaw, face, hand, trunk, leg, foot, and other movements. His utterances and selection of levers were recorded. The subject was repeatedly asked about his feelings, and whether or not he felt frustrated, angry, or hopeless. Responses to failure were scored in four successive stages (Table 5).

TABLE 5.—*Behavior During Repeated Failure*

Stage 1
Continued goal-directed searching
No perserveration of responses
Motor activity limited to purposive lever pressing
(Scored 0)
Stage 2
Continued goal-directed searching, alternating with perseveration of response
Widespread and increased motor activity
Utterance and show of anger and frustration
(Scored 1 point for each perseveration)
Stage 3
Abandoning of goal-directed searching
Perseveration of response
Slumped, posture-listless movements; utterances and show of discouragement, frustration, "giving up"
(Scored 6 points for each perseverative movement)
Stage 4
Abandoning of keyboard
Complete immobility
Posture slumped — head on arms
Utterances and show of hopelessness and despair
(Scored 50 points for each minute of Stage 4)

Under the scoring system used, the poorest performance was scored at 800 points.

Normal (control) data for the above-described laboratory procedures were based on (1) the published reports for the Wechsler aggregate, derived from Wechsler's normative data; (2) a personal communication from Halstead on previously obtained data from 250 intact young subjects and a sample of 25 intact laboratory and clerical workers (see "Appendix"), using this aggregate of test procedures; (3) data obtained in this laboratory for the conditioning and reaction-to-failure procedures; (4) data previously obtained from the responses of 25 intact subjects to the Rorschach test.

The assay procedures were applied to 132 subjects with damage of the cerebral hemispheres who met the above-described conditions. The amount and site of loss of cerebral hemisphere tissue could be estimated reliably in 60 subjects (Table 6). Of these; 27 subjects had had focal and nonprogressive cerebral disease, i. e., from one to eight years after surgery; 33 subjects with brain tumors requiring excision were studied shortly before and three weeks to one month after surgery. The amount of loss of hemispheric tissue, while not measurable precisely, could be estimated with sufficient accuracy in most instances to permit generalizations about the mass of tissue.

Sketches of the region of the cerebral hemispheres from which tissue was removed and extent

TABLE 6.—*Subjects with Brain Defects: Their Site, Side, and Nature*

Case	Age	Schooling, Yr.	Time Since Operation, Mo.	Pathological Diagnosis	Site	Size *	Side	Occupation
1	34	12	7	A. V. anomaly	Occipital-parietal	D	R	Seamstress
2	59	8	6	Mengingioma	Frontal	A	L	Dietician
3	22	12	70	A. V. anomaly	Occipital	B	R	Coil winder
4	50	8	38	Meningioma	Temporal	D	R	Domestic
5	56	8	68	Meningioma	Frontal	B	L	Factory machine operator
6	51	12	8	Meningioma	Frontal	D	R	Secretary
7	38	11 ½	34	A. V. anomaly	Parietal	A	L	Office manager
8	57	17	56	Meningioma	Parietal	B	L	Lawyer
9	37	11	5	Meningioma	Frontal	B	R	Factory machine operator
10	20	8	48	Tuberculoma	Occipital	C	R	Retail sales clerk
11	27	12	42	A. V. anomaly	Occipital	B	R	Machinist
12	58	14	54	Meningioma	Frontal	C	R	Schoolteacher
13	44	12	29	Meningioma	Frontal	D	B	Bookkeeper
14	46	8	25	Meningioma	Temporal	C	L	Railway brakeman
15	56	16	44	Oligodendroglioma	Parietal-occipital	D	R	Journalist
16	34	12	87	A. V. anomaly	Parietal	A	L	Fireman
17	44	6	27	Astrocytoma	Frontal	E	R	Gardener
18	49	14	15	Astrocytoma	Frontal	E	L	Salesman
19	17	11	54	A. V. anomaly	Occipital	B	R	Student
20	40	12	69	Meningioma	Frontal	B	R	Dental assistant
21	27	12	16	Astrocytoma	Frontal	E	L	Machinist
22	35	12	69	A. V. anomaly	Frontal	D	R	Secretary
23	52	12	22	A. V. anomaly	Occipital	B	R	Retail sales clerk
24	48	5	56	Meningioma	Frontal	E	B	Factory machine operator
25	19	10	7	Astrocytoma	Frontal	E	R	Factory machine operator
26	35	20	1	Meningioma	Frontal	B	R	Surgeon
27	39	20	1	Astrocytoma	Frontal	D	R	Psychiatrist
28	42	8	1	Meningioma	Frontal	C	R	Factory machine operator
29	34	16	1	Meningioma	Occipital-parietal	D	R	Bookkeeper
30	38	9	1	Carcinoma	Parietal	B	R	Elevator operator
31	35	9	30	A. V. anomaly	Frontal	C	L	Interior decorator
32	34	8	48	Hemangioma	Parietal	C	R	Plumber
33	52	7	36	Meningioma	Frontal	C	L	Messenger
34	38	13	96	Meningioma	Frontal-parietal	B	L	Bank clerk
35	57	12	72	Meningioma	Frontal	E	R	Retail sales clerk
36	60	8	60	Meningioma		D	R	Salesman
37	39	20	1	Astrocytoma	Frontal	E	R	Dentist
38	30	20	1	Glioblastoma †	Temporal	C	R	Internist
39	37	17	1	Cortical scar frontal	Frontal	D	R	Sales manager
40	60	16	1	Meningioma	Temporal	A	R	Diplomat
41	39	8	2	Hemangiosarcoma	Parietal	A	R	Office manager
42	60	6	4	Ependymoma	Parietal	B	L	Seamstress
43	61	4	1	Metas. carc. lung †	Parietal	C	L	Porter
44	45	10	1	Astrocytoma	Frontal	A	L	Restaurant manager
45	60	8	1	Meningioma	Frontal	E	R	Taxi driver
46	56	16	1	Glioblastoma †	Temporal	D	R	Schoolteacher
47	45	6	24	Meningioma	Temporal	B	R	Miner
48	48	16	1	Meningioma	Frontal	B	L	Accountant
49	50	16	1	A. V. anomaly	Occipital	D	R	Secretary
50	50	8	1	Meningioma	Parietal	E	R	Factory mach. worker
51	19	7	24	A. V. aneurysm	Parietal	E	L	None
52	31	13	4	A. V. anomaly	Parietal	B	L	Accounting clerk
53	51	4	1	Ependymoma	Parietal	E	R	Porter
54	50	13	18	Meningioma	Temporal	A	L	Piano teacher
55	38	10	1	Meningioma	Parietal	B	L	Retail sales clerk
56	55	16	1	Astrocytoma	Temporal	E	L	Schoolteacher
57	25	12	1	Meningioma	Frontal	E	L	Housewife
58	45	12	1	Meningioma	Frontal	B	L	Housewife
59	60	8	1	Glioblastoma †	Frontal	E	R	Housewife
60	50	12	1	Meningioma	Frontal	E	R	Housewife

* A=up to 30 gm.; B, 30 to 60 gm.; C, 60 to 90 gm.; D, 90 to 120 gm.; E, 120 to 150 gm.

† The nodules of metastatic carcinoma in the brain are accompanied by conspicuous edema, making the assessment of extent of lesion especially difficult; however, the estimate of mass of tissue loss was based on the extent of the area resected, which was larger than the mass of the nodule. Also, since both metastatic carcinoma and glioblastoma are progressive, these subjects were studied only in the period from three to six weeks following surgical treatment.

of removal were made by the surgeons § on standard drawings of the brain in four views. From those sketches, and from the weight of removed specimens, an estimate of the total extent of damage to the brain (both from the pathological process and from the surgical procedures) was made. This estimate was then converted into the mass, in grams, that would be lost by similar removal from a standard 1,400 gm. formalin-fixed brain (Table 7). For convenience of discussion and charting, and because at best such estimations could be only approximately correct, the lost amounts of brain tissue were expressed in units of 30 gm. Thus a patient who had suffered an estimated loss of 25 gm. according to the above method of assay would be placed in Category A, or with those who had lost from 1 to 30 gm. of cerebral hemisphere; a patient with an estimated loss of 40 gm. would be placed in Category B, or with those who had lost from 30 to 60 gm. of tissue, etc. For calculations involving the lesion mass, the midpoint of the category was used to express the individual lesion mass, i. e., 15 gm. for Category A, 45 gm. for Category B, etc.‖

§ We are much indebted to Dr. Bronson Ray and his staff, Dr. Fremont C. Peck, Dr. Henry L. Hood, Dr. Russel H. Patterson, and Dr. Edward P. Ryan, for their help in defining the site and mass of loss of cerebral tissue.

‖ Marcia Rossett gave technical assistance in the laboratory assessment of these patients.

TABLE 7.—*Weight of Various Portions of the Human Brain*

Average of determinations on three brains. The weights are adjusted proportionally to a standard total brain weight of 1,400 gm.

	Gm.
Total brain	1,400
Cerebellum	162
Brain stem (medulla oblongata) from approximately the level of the first cervical segment to level of red nucleus	40
Cerebral Hemispheres	
Sections are made perpendicular to the longitudinal axis	
Frontal lobe	**Gm.**
1. 2 cm. from anterior tip	22
2. 4 cm. (at genu of corpus callosum)	55
3. 4.5 cm. (at tip of anterior ventricle)	78
4. 6 cm. (through Broca's area)	124
5. 7 cm. (to precentral gyrus, includes cingulum but not caudate nucleus)	153
6. Entire lobe (back to central sulcus, including precentral gyrus, and the orbital and opercular portions of the frontal lobe, but not including thalamus, basal ganglia, or corpus callosum)	209
Temporal lobe	**Gm.**
1. 2 cm. from anterior tip (measured along lateral surface)	10
2. 4 cm. (including parts of uncus, hippocampus, and amygdaloid nucleus, at tip of temporal horn of ventricles)	27
3. 6 cm. (includes hippocampus)	47
4. 8 cm.	73
5. 10 cm. to paraoccipital notch	100
Parietal lobe	**Gm.**
1. Cingulum	5
2. Insula	9
3. 1 cm. posterior to central fissure (spares insula and cingulum)	13
4. 2 cm. (spares insula and cingulum)	36
5. 3 cm. (spares insula and cingulum)	62
6. 4 cm. (spares insula and cingulum)	81
7. 6 cm. (spares insula and cingulum)	138
Occipital lobe	**Gm.**
1. 2 cm. anterior from posterior tip	12
2. 4 cm.	33
3. 5.5 cm. (entire lobe through parieto-occipital fissures)	70
Summary (1,400 gm. brain)	
	Gm.
One frontal lobe back to central fissure	210
One temporal lobe back to paraoccipital notch	100
One parietal lobe	138
One occipital lobe	70
Total	518

TABLE 8.—*Summary* of Extralaboratory Ratings*

Subject	Mass, Gm.	Site †	Rating	Mean
2	15	F	42	
7	15	NF	30	36
16	15	NF	35	
5	45	F	45	
9	45	F	53	
20	45	F	30	
26	45	F	24	
8	45	NF	63	40
19	45	NF	32	
23	45	NF	28	
3	45	NF	35	
4	45	NF	50	
11	45	NF	40	
12	75	F	51	
28	75	F	88	
10	75	NF	62	71
14	75	NF	82	
16	105	F	80	
13	105	F	72	
22	105	F	24	
27	105	NF	60	62
1	105	NF	75	
15	105	NF	63	
17	135	F	94	
18	135	F	51	
21	135	F	83	76
24	135	F	67	
25	135	F	87	

* Sum of ratings of from 1 to 5 for the 20 criteria in Table 1.

† F=frontal lobe; NF, parietal, occipital, or/and temporal regions.

Results

1. Study of Performance of Subjects with Focal Loss of Tissue from the Cerebral Hemispheres Up to 150 Gm.

A. Assessment of Behavior in Natural Setting (Extralaboratory)

On the basis of the interviews with the subjects, their families, and associates, impairment of over-all adaptive capacity in their home, work, and community setting was assessed. Table 8 indicates the results of the ratings for the 20 criteria of impairment. Impairment scores were related to the mass of the defect, regardless of site.

The observed signs of faulty function of the cerebral hemispheres ranged from the day to day fluctuations in capacity that healthy persons recognize in themselves to grossly apparent defects in orientation, memory, and judgment. Several stages of decline with increasing loss of tissue mass could be discerned, although the changes were on a continuum with fluctuations from hour to hour and day to day, with periods of improvement when circumstances were propitious and rapid decline when they were not.¶

Phase 1

In this early stage of waning cerebral hemisphere function, there was a reduction in adaptive versatility and the capacity to maintain adaptive function during stress. Characteristically, there was less spontaneity and "sparkle." These persons were slower and exhibited less energy, drive, and initiative. This was described in phrases that indicated that they were "slowed up," subdued, or "seemed less of a person." They lacked "snap" and "go," and it became increasingly difficult for them to persist in doing a task. They complained of becoming tired more readily when applying themselves to a given task, or after sustained effort. Learning new skills or facts, or making discriminations was difficult, fatiguing, and exhausting. They talked less, and less well. They were "slow on the uptake," as in catching the point of an anecdote, joke, or allusion. Some made occasional unrestrained comments or criticisms. They were less active physically, and many gave up routine or daily athletic activity and weekend social activities. They showed little or no interest in social activities, such as parties or "cocktails," and many were even exhausted and made unhappy by the effort of superficial social exchange. Their capacity for imagery and for association dwindled. They had fewer "hunches," and their intuitions were less good. They were more readily angered, and their capacity to endure frustration was decreased. They avoided family reunions, social organization meetings, and casual "dropping in." They gave out less, radiated less warmth, and even seemed "cold." They were definitely less interested in people—their views, attitudes, and utterances. Their expressions of endearment, encouragement, and love were fewer. Whereas there was lessened show of affection, warmth or sensitivity to the feelings of others and little concern for the well-being of friends and even of the family, there was on the other hand, sometimes an assertion of the importance of early learned principles of behavior. This gave the impression that the subject was impersonal though correct in his adherence to his value system. (Such reliance on early learned broad principles and generalizations seemed to be a feature of the subject's avoidance of conflict.)

They failed to "keep up" with current events. They sought and preferred the familiar, and shunned and avoided the unfamiliar, the strange, and the new. They attempted to define and limit their sphere of activity within a routine that insured ready success. They had little patience over delays. In general they needed more time for rest and recuperation before being able to perform a task previously done correctly. The buffeting of the day's affairs left them more exhausted than before. Their interest in sexual intimacy fell off. Failures, frustrations, deprivations, postponements, unfulfilled goals, and difficult discriminations

¶ The complete protocols of these patients will be presented in a forthcoming monograph.

and decisions produced irritability, fatigue, and anxiety, from which it took longer to recover. Situations and memories previously innocuous resulted in anxiety, and the capacity to be effective in the face of anxiety was reduced.

They tried to do one thing at a time, and rapid shifts from one role or problem to another became very difficult, if not impossible. Interviews were shortened, appointments broken. There was increasing difficulty in eliminating or extinguishing irrelevant stimuli and in concentrating on the pertinent and deleting the irrelevant. Noises bothered them more than usual; crowds or public places were disturbing. Persons with a broad range of interests found them lessened, and, indeed, interests in any topic were not well sustained, even in the favorite or central topic of work or creative life. Creative activity dwindled. Sustained efforts necessary for it fell off, and the "taking of endless pains" was not evident. They were less alert in seeing errors or faulty conclusions. These subjects were aware of their decline in capacity and hence became more anxious, and sometimes depressed. The prevailing premorbid defenses were much more conspicuous. Goals and purposes * continued to be pursued, although obviously less effectively and at greater cost. Amounts of alcohol that premorbidly were consumed for pleasure now caused the patients to feel intoxicated and lethargic.

Persons with focal damage of the order approximately 30 to 60 gm. of cerebral hemispheric tissue commonly exhibited Phase 1 impairment.

Phase 2

Most of the defects described in Phase 1 were present in Phase 2, and were more conspicuous and striking. These subjects were much slower in speech, understanding, and action. There was greater difficulty in seeing the implications of events, in extrapolating, and in deriving inferences or consequences. Spouses, friends, and employers found that the judgment of the subjects was less good, especially in new situations. Greater difficulty was encountered with the making of decisions and in initiating plans. Conscientious attention to detail was less in evidence, and the subjects often let important matters "ride" or indefinitely postponed action upon them.

The fulfillment of personal ambitions and social responsibilities seemed less important, but increased anxiety and depression accompanied an awareness of dwindling capacity. When anxiety thus was increased greatly, the fall-off in highest-level functions was increased. Defense reactions were integrated less well and were modulated poorly. The subjects became increasingly self-absorbed, and their main concern was with their own interests. They became insensitive to the feelings and reactions of others. Recall was delayed; calculation was labored, and persistent effort became increasingly difficult. Family and friends sometimes assumed that the patients did not hear well, because of their poor comprehension of speech.

Frustration threshold and tolerance were even more evidently lowered in these patients than in those with Phase 1 impairment. Situations that might lead to failure were avoided, as were responsibility, decision making, or situations calling for incisive action. Irritability and temper outbursts were striking if such avoidance was not possible. The patients sometimes did not sleep well, and sleep was less refreshing.

Alcohol and sedatives and analgesic drugs had more striking, depressive effects and were usually avoided voluntarily by the patients.

Persons with focal damage of approximately 60 to 90 gm. commonly exhibited Phase 2 impairment.

Phase 3

Most of the family, friends, employers, and associates recognized in this phase that "something is radically wrong." "He is a changed person; he is a different man; after

* The word "purpose" is used as Sinnott [178] defines it, as "another name for the self-regulatory and goal-seeking character of protoplasm. . . ."

not meeting him for some time, I did not believe it was the same person," were common descriptive remarks. The subjects were less and less interested in what people thought of them. Their behavior sometimes was unrestrained, impulsive, aggressive, facetious, or brash, and they were less sensitive to social restraints and forms. Jocularity and ebullience sometimes occurred. Dress often was inappropriate, and they were less neat, clean, and orderly. The capacity to perform several acts concurrently was lost. Meal hours were delayed if the patient prepared the meals. The menus were unpredictable—in excess at one time, sparse in another. Activities and thoughts were slow and labored. Directions had to be given slowly and repeatedly. Inaccuracies and inconsistency were not recognized. These subjects were "inert" and needed to be pushed and given a degree of momentum before activity started. Memory for the recent past was poor or failing, whereas remote memory was for the most part good. Learning ability was very poor, and adjustment to new surroundings or new associates was difficult and slow and produced bewilderment and fears. Orientation about time was poor, especially for the hours of the day and the day of the week. Appointments were poorly kept and might be forgotten or mixed, so that the subjects appeared at one place when they should be at another. In relating incidents or replying to questions, their statements were "drawn out" in time. They were circumstantial about the past, lost the thread of an account, related irrelevant or minor details at length, wandered, stopped, or dawdled, and often needed to be started again with a new question. Anxiety, which in the subjects described under Phases 1 and 2 was often augmented, in most instances was strikingly diminished in Phase 3. The patients' emotional expressions, sometimes with euphoria, punning, wisecracks, and silly jokes, were thin, and their facial expressions and gestures gave them a "wooden" quality. They showed little warmth or love, although they might repeat old, established phrases of endearment. Inertia and lethargy were conspicuous, and the subjects might fall asleep in the middle of a conversation or in social situations. They had difficulty in following directions, could not engage in a general conversation involving abstract topics, and could not understand what was going on when several people were speaking or there was a cross current of conversation. The patients complained of difficulty in thinking, and their attention span was shortened.

The prevailing premorbid defensive reactions became conspicuous, poorly modulated, transparent, splintered, silly, and socially unacceptable. Persons with conspicuous defensive reactions before the loss of brain tissue now, because of the distortion of those reactions, might be adjudged psychotic.

The appetites and drives, though not strong, would be sometimes inappropriately exhibited. Obscene or profane humor sometimes was complained of by those around them. Restlessness and overactivity was characteristic of the behavior of some, but extreme fatigability and exhaustion were commoner. There was often overreaction to brief noxious stimulation but indifference to sustained stimulation. Business activities or investments sometimes ended in catastrophe, and wills were changed impulsively and foolishly. These subjects were readily exploited by unscrupulous persons. Delirious reactions were induced far more readily by exhaustion, starvation, drugs, infection, fever, removal to unfamiliar or isolated surroundings, or restrictions of sensory stimulation (putting to bed, binding of eyes with bandages, etc.)

However, even after the loss of as much as 100 gm. of tissue from the cerebral hemispheres, some subjects were able to continue with their usual work activities, although in a modified manner. They did less well in home and community circumstances; they were ostensibly less demanding, but actually more so, because of their

unstructured and unpredictable nature. Outstanding in the series were persons who premorbidly demonstrated adequate adaptive capacity and who had been especially proficient in a skill, profession, or technical "know-how." A psychiatrist, a lawyer, a surgeon, and a newspaper columnist all continued their professional activities on a full-time basis following the loss of from 45 to 100 gm. of tissue from the cerebral hemispheres (frontal lobe, parietal lobe, frontal lobe, parieto-occipital region, respectively). Tasks requiring the development of new skills, spontaneity, high order of judgment, and unexpected demands were avoided by these patients. They husbanded their energy, employed memory aids, and established stable routines. They avoided social and interpersonal situations that were likely to require a show of feeling or a new adjustment. All complained that situations that premorbidly would have evoked strong feelings now engendered a rapid disorganization of existing capacities and were especially disturbing because of the subjects' uncertainty about their capacity to modulate the expression of feelings appropriately.

Persons with focal damage of approximately 90 to 120 gm. commonly exhibited Phase 3 impairment.

Phase 4

These patients were frankly "demented" and were recognized as such by everyone. They were apathetic, and their features and behavior had a "zombie-like" quality, although they might repeat established pleasant phrases and thus conceal the emptiness of personality and mentation. The usual bedside examination of mental status readily exposed defects. Orientation was poor in all spheres, most strikingly in regard to time. Parts of the body were recognized poorly, and right and left differentiation became difficult. Placing the right index finger on the left ear might not be possible, whereas the command "show me your right index finger" evoked correct response. Vocabulary was adequate, and early factual information was in part retained. Remote, and especially recent, memory dwindled. Calculation was grossly defective, and there was no recognition of defects. There was indifference to persons in their vicinity. They exposed themselves indifferently, lost the social amenities, and ate too little or too much, the amount often depending on how much was immediately available. When uncomfortable with cold or warmth, they did not correct the situation. Retention was poor, and a series of three or more simple directions could not be remembered. A story with several detailed incidents could not be recalled immediately after hearing it. Confabulation might be striking, and suggestibility increased. They could do only one thing at a time and had lost many skilled acts. They were indifferent about personal cleanliness. There was perseveration of phrases, utterances, and motor acts. Catatonic postures and waxy flexibility were sometimes exhibited. Talking was often excessive and noisy, and occasionally there was tireless or restless overactivity. The patients were relatively indifferent to sustained noxious stimulation. Indeed, most painful stimuli, threatening circumstances, catastrophic events, or even impending death had lost significance and caused little reaction. On the other hand, sudden noxious stimulation often evoked an over-reaction of crying, rage, or violence. Passivity was often conspicuous; nonadult patterns of complaint and attention-seeking prevailed, requiring nursing care like that given to infants. Perceptions of all sorts were reduced, slowed, blurred, and distorted. Misinterpretations followed, although hallucinations as such were uncommon. There was loss of interest in food, sexual intimacy, bodily warmth, and preservation of self and kin. Tremor was often conspicuous and movements awkward.

Anxiety was minimal, and defensive and compensatory reactions were inadequate or no longer maintained. Failure or frustration led to further rapid disorganization of the remaining high-level functions, whereas a

show of kindliness and fulfillment of wants brought out optimal performance.

Persons with focal damage of approximately 120 to 150 gm. or more commonly exhibited Phase 4 impairment.

Comment

The following generalizations and formulations epitomize the data regarding adaptive behavior after focal loss of tissue from cerebral hemispheres.

The subject's prevailing premorbid defenses were preserved in general form and were exhibited, especially during periods of stress. However, after loss of cerebral hemisphere tissue the defensive and compensatory reactions were less well organized, less well sustained, and less effective in maintaining tranquility and permitting continued fulfillment of social and interpersonal responsibilities. This led to behavior that was less aceptable socially, more highly personalized, and sometimes bizarre. The degree of impairment in the capacity to maintain effective defenses, although linked to the mass of the tissue loss, was not related to the site of the tissue loss within the cerebral hemispheres.

Several factors increased the need for effective defenses after cerebral hemisphere tissue loss. 1. New situations had to be met with a now-reduced mechanism for the achievement of goals. 2. Thresholds for "deprivation" and "frustration" were lower, as evidenced by increased seeking of support, encouragement, praise, and approval and a ready show of anger, discouragement, and "giving up." 3. Disorganization following frustration, deprivation, failure, and conflict was severer and longer-lasting. In subjects in whom moderate (up to 60 gm.) amounts of cerebral hemisphere tissue had been lost, an exaggeration of the defenses and an increase in anxiety were more frequently observed than were reductions in defense reactions and anxiety.

On the other hand, several features of the effects of loss of cerebral hemisphere tissue were relevant to the reduced expression and maintenance of defenses in persons with large lesions (more than 90 gm.): (1) a reduction in the capacity for intense and sustained affective response; (2) impairment in the capacity to perceive threat, as evidenced through utterances and behavior, and (3) a reduction in the need for environmental challenge, which permitted the adopting by many subjects of a more simple, less demanding, and more predict-

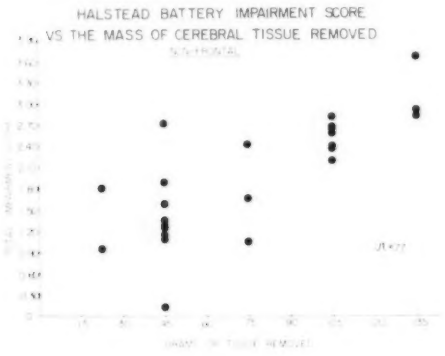

Figure 1

Fig. 1.—Total impairment scores (mean of the standard scores for the 10 components) for the Halstead Aggregate of 24 subjects with lesions in the parietal, occipital, or temporal lobes, as related to mass of tissue loss. The correlation coefficient for mass of tissue loss and impairment score was 0.77. This degree of correlation would be expected to occur by chance fewer than 1 time in 100. The impairment scores are expressed in units of the number of standard deviations (calculated for the intact group) from the mean of the intact group.

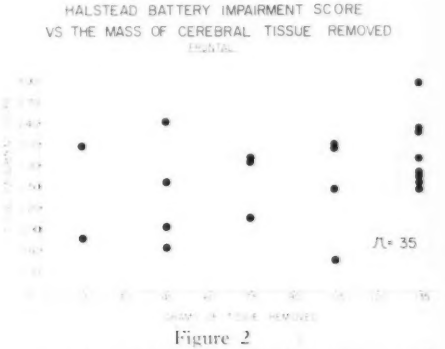

Figure 2

Fig. 2.—Total impairment scores (mean of the standard scores for the 10 components) for the Halstead Aggregate of 21 subjects with lesions in the frontal lobes, as related to mass of tissue loss. The correlation coefficient for mass of tissue loss and impairment score was 0.35. This degree of correlation would be expected to occur by chance oftener than 5 times in 100.

TABLE 9.—*Halstead Aggregate* *

Subjects	No.	Age, Yr.	Schooling, Yr.	Impairment Score	
				Mean	S. D.
Small frontal	9	45.2	11.1	1.45	0.60
Large frontal	12	42.5	11.9	1.80	0.58
Small nonfrontal	14	35.3	11.6	1.53	0.50
Large nonfrontal	10	46.0	10.8	2.68	0.40
All frontal	21	43.7	11.6	1.65	0.62
All nonfrontal	24	39.8	11.3	2.01	0.73
All small	23	39.2	11.5	1.50	0.54
All large	22	49.1	11.4	2.20	0.67
All subjects	45	41.6	11.4	1.84	0.70

Analysis of Variance for the Impairment Score

Source	*d. f.*	Sum of Squares	Mean of Squares	*F*
Site	1	14,843.4349	14,843.4349	4.89 †
Mass	1	54,536.1054	54,536.1054	17.95 ‡
Interaction	1	27,710.0565	27,710.0565	9.12 ‡
Error	42	124,566.9810	3,038.2190	
Total	45	221,656.5778		

* The total impairment score for the Halstead Aggregate was calculated as follows: 1. Tables for each of the 10 components were constructed which allowed the conversion of raw scores for each component into standard impairment scores expressed in units of the standard deviation of the intact group from the mean of the intact group (the positive or negative sign for each score was arranged so that a positive sign signified poorer performance: the scores better than the mean of the intact group were assigned an impairment score of 0, ** and scores more than 4 standard deviations from the mean were assigned a score of 4.0). 2. A total impairment score was derived by calculating the mean of the standard impairment scores for each of the 10 components.

F ratios (a comparison of the degree of variation between the scores of the groups, large *vs.* small or frontal *vs.* nonfrontal, with the degree of variation within the groups) were calculated in the analysis of variance. The *F* ratio for mass (small, less than 90 gm. *vs.* large, 90-150 gm.) was 17.95, indicating with a high degree of confidence that the performance of subjects with large lesions was poorer than the performance of those with small lesions. The probability that this *F* ratio would occur by chance is much less than 1:100. The *F* ratio for site (frontal *vs.* nonfrontal) was 4.89, indicating with a fair degree of confidence (5% level) that as a group subjects with nonfrontal lesions performed less well than did those with lesions in the frontal lobes. However, inspection of the mean score of the various groups indicates that this difference was observed only for patients with large lesions. The mean score of the "small nonfrontal" group was approximately equal to that of the "small frontal" group, whereas the mean score of the "large nonfrontal" group indicated a much poorer performance than that of the subjects in the "large frontal" group.

Thus, while site of lesion did not influence impairment scores for subjects with up to 90 gm. tissue loss, it did influence the scores of those with lesions larger than this. From this analysis it would be expected that the *F* ratio for the joint expression of site and mass (site×mass interaction) would be significant. This is borne out by the calculated *F* ratio of 9.12 for interaction, a ratio that would be expected to occur by chance fewer than 1 time in 100.

** It is to be noted that the convention of assigning an impairment score of 0 to performances better than the mean of the intact group has the effect of biasing the distribution of the scores. This bias would be in the direction of giving higher impairment scores to groups in which a significant proportion of subjects scored better than the mean of the intact subjects than to groups in which few subjects scored better than the mean of the intact subjects.

† Significant at 5% level.

‡ Significant at 1% level.

able way of life. This relative reduction in intensity of defense reactions was observed most frequently in those whose premorbid patterns had been characterized by excessive striving, "rumination," self-blaming, and guilt; in those subjects anxiety was diminished as well.

B. Assessment of Highest-Level Functions by Means of Laboratory Procedures #

The performances of these subjects on the Wechsler-Bellevue Aggregate, the Halstead Aggregate, the conditioned-reactions procedure, and the scoring of the responses to the Rorschach Ink Blots procedure are presented in Tables 9 to 16, and in Figs. 1-19. It can be seen that, despite wide variations in the performance of those with defects of a given size, a significant relationship was observed between the degree of impairment and the mass of tissue loss in the range studied (between 15 and 150 gm.). The degree of defect in these subjects was not related to site of tissue loss within the hemispheres in subjects with loss of up to approximately 90 gm. of tissue, except, for

The authors are grateful to Samuel Lyerly, Ph.D., for advice and assistance in the statistical analysis of these data.

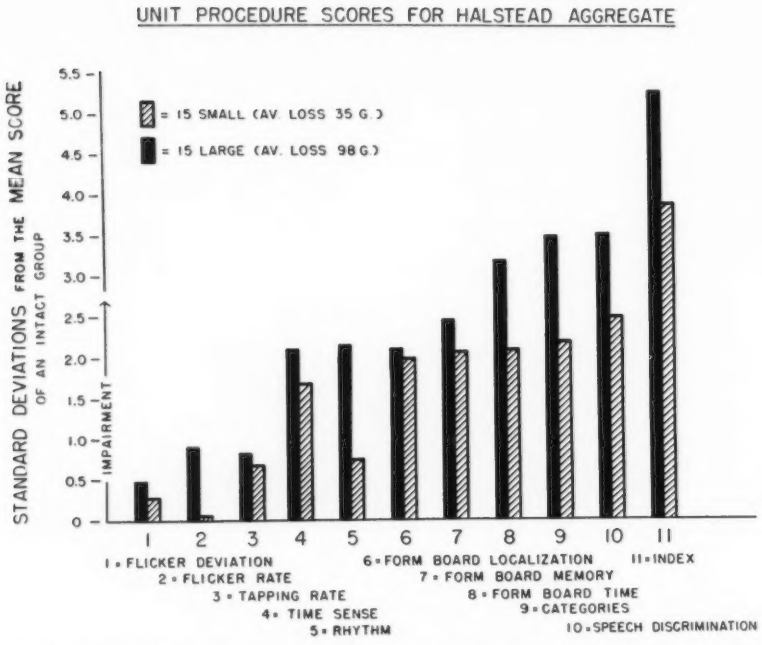

Fig. 3.—Average (mean) scores of the individual components of the Halstead Aggregate for 15 subjects with loss of small (less than 60 gm.) amounts of cerebral hemisphere tissue compared with the average scores for 15 subjects with loss of large (60-150 gm.) amounts of tissue. Scores are expressed as deviations from the mean of intact (control) scores (in units of the standard deviation of the intact scores for that procedure). The two groups are matched in terms of average age, average years of education, etc.: number of subjects, S (small) 15, L (large) 15; dominant side, S 9, L 9; nondominant side, S 6, L 4; bilateral, S 0, L 2; more than six months after tissue loss, S 12, L 11; less than two months after tissue loss, S 3, L 4; mean age, S 42.0, L 42.8; mean years of education, S 11.6, L 11.8; mean mass of tissue loss, S 35 gm., L 98 gm; frontal lobe site, S 6, L 7; nonfrontal lobe site, S 9, L 8.

the responses to the Rorschach Ink Blots, which were scored as more impaired for the subjects with loss of tissue from the nonfrontal regions. On the other hand, subjects with loss of more than 90 gm. tissue from the nonfrontal regions performed less well, mass for mass, than did those with loss of a comparable mass of tissue from the frontal lobe. Since virtually all of the assay procedures mentioned above are dependent upon visual skills, this greater impairment in the subjects with large (more than 90 gm.) nonfrontal lesions probably is a reflection of the major impairment of vision present in these subjects. This difference is considered to be an example of impairment of a lower-level function, that is, related to site of tissue loss (in this instance, vision) affecting the performance scores on procedures designed to assess the highest integrative functions which are not related to site of loss within the hemisphere.

The Capacity to Withstand Repeated Failure

An experimental situation which was designed to be uniformly and maximally frustrating was devised, and observations were made of behavior under circumstances of repeated failure with the method described on page 375.

Intact Group

In the intact group 30 subjects were included.

TABLE 10.—*Summary of Analysis of Variance for the Components of the Halstead Aggregate* *

	F			
	Over-All	Site	Mass	Interaction
1. Categories	3.5 †	1	3.1	6.5 †
2. Flicker rate	6.9 †	8.0 †	12.3 ‡	1
3. Flicker deviation	1	1	1	1
4. Form board time	3.9 †	1	6.83 †	8.51 ‡
5. Form board memory	2.79 †	4.00	1	3.39
6. Form board localization	1.14	2.45	1	1
7. Rhythm	3.85 †	1	8.49 †	2.74
8. Speech	1	1	1	1
9. Tapping	1	1	1	1
10. Time est.	1	1	1	1
11. Total impairment score	10.65 ‡	4.89 †	17.95 ‡	9.12 †

Means, Standard Deviations, and Correlations (*r*) with Lesion Mass

	1	2	3	4	5	6	7	8	9	10	11
Small frontal											
Mean	3.16	0.44	0.48	2.03	1.78	1.78	1.51	2.20	0.48	0.60	1.45
S. D.	1.30	0.74	0.54	1.81	1.53	0.82	1.06	1.37	0.49	1.28	0.60
Large frontal											
Mean	2.74	1.72	0.37	2.35	1.61	1.62	1.83	2.43	1.17	2.16	1.79
S. D.	1.14	1.05	0.44	1.54	1.23	0.89	1.00	1.61	1.23	1.86	0.58
All frontals											
Mean	2.92	1.17	0.41	2.21	1.68	1.69	1.70	2.34	0.87	1.49	1.65
S. D.	1.23	1.12	0.48	1.67	1.37	0.86	1.04	1.51	1.04	1.81	0.62
r	−0.101	−0.521	−0.148	0.241	−0.005	0.048	0.238	0.026	0.311	0.410	0.350
Small nonfrontal											
Mean	1.97	0.30	0.22	1.60	2.00	1.92	0.91	2.01	0.90	1.79	1.54
S. D.	1.21	0.51	0.46	1.59	1.28	0.68	1.06	1.60	0.04	1.70	0.50
Large nonfrontal											
Mean	3.45	0.67	0.36	3.74	3.13	2.20	2.36	3.47	1.61	2.37	2.68
S. D.	1.78	0.89	0.55	0.78	0.95	0.33	0.92	0.97	1.06	1.51	0.41
All nonfrontal											
Mean	2.59	0.45	0.28	2.49	2.47	2.04	1.52	2.62	1.20	2.14	2.01
S. D.	1.28	0.72	0.50	1.68	1.28	0.57	1.23	1.55	1.10	1.64	0.73
r	0.577	0.113	0.128	0.531	0.512	0.177	0.530	0.523	0.466	0.242	0.771
All subjects											
Mean	2.74	0.79	0.34	2.36	2.10	1.89	1.60	2.49	1.05	1.84	1.84
S. D.	1.27	0.99	0.50	1.68	1.38	0.75	1.15	1.54	1.09	1.75	0.70
r	0.263	0.403	0.022	0.358	0.169	0.044	0.398	0.250	0.344	0.278	0.499

* The *F* ratios for site were significant only for flicker fusion rate and for the total impairment score. The total impairment score is presented in Table 9. The flicker fusion rate was lower for subjects with frontal lobe lesions; this observation confirms the previous observation of Halstead[1,2,3] that critical flicker frequency is reduced to a greater extent in subjects with lesions of the frontal lobes than it is in subjects with lesions of comparable extent elsewhere in the cerebral hemispheres. It is difficult to assess the relationship of this procedure to the highest integrative functions. Halstead has related it to his "power" factor in biological intelligence, but on the surface it appears to be linked more closely with simpler perceptual tasks. The *F* ratios for mass were significant for flicker fusion rate, form board time, the rhythm test, and the total impairment score. The significant *F* ratios for interaction (categories, form board time, and the total impairment score) reflect the greater impairment in subjects with large nonfrontal lesions than in those with large frontal lobe lesions.

† Significant at 5% level.

‡ Significant at 1% level.

After one to three buzzers, all 30 control subjects demonstrated a Stage 2 response, with increased motor activity but without perseveration in most, so that 20 scores in this group were 0. Four subjects showed intermittent perseveration of a wrong response associated with a period of increased motor activity, and six demonstrated brief periods of reduced activity with intermittent perseveration or immobility. The average impairment score for the control group was 19.

In general, the intact subjects performed in a predictable manner in the experimental failure situation. Whereas all these subjects verbalized feelings of failure in performing

this seemingly simple task and described feelings of anger and resentment, they nevertheless continued goal-seeking. They reported being aware of their increased purposeless movements and often regarded the motor activity as part of their effort to improve their performance. A few subjects described strong feelings of hopelessness or despair, but none decided to "give in" or to "give up." All stated that they would have continued their attempts to solve the problems even much longer. All made remarks emphasizing how poorly they had done.

Focal lesions (26 subjects; Fig. 20)

Twenty-six subjects had focal lesions. There were three subjects with *A* lesions (0-30 gm.), six subjects with *B* lesions (30-60 gm.), seven subjects with *C* lesions (60-90 gm.), three subjects with *D* lesions (90-120 gm.), and seven subjects with *E* lesions (120-150 gm.) or more.

The three subjects having the smallest, or *A*, lesions, showed no defects on the failure procedure other than transient, short-lasting perseveration. In similar fashion, the six subjects with *B*, or 30-60 gm., lesions, showed in four experiments only transient perseveration and, on one occasion only, short-lasting reduced activity (Stage 3). Scores were similar to the control group's.

Of the seven subjects having *C*, or 60-90 gm., cerebral lesions, six persons showed perseveration, and three subjects demonstrated reduced activity of Stage 3, lasting

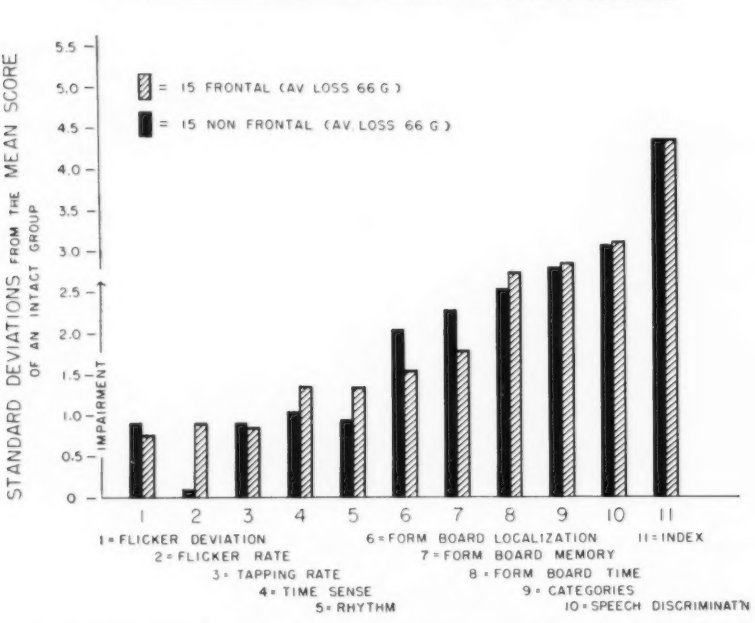

Fig. 4.—Average (mean) scores of the individual components of the Halstead Aggregate for 15 subjects with loss of cerebral hemisphere tissue from the frontal lobes compared with the average scores of 15 subjects with loss of tissue from the parietal, temporal, or occipital. Scores are expressed as deviations from the mean of intact (control) scores (in units of lobes. the standard deviation of the intact scores for that procedure). The two groups are matched in terms of average age, average years of education, etc.: number of subjects, F (frontal) 15, NF (nonfrontal) 15; dominant side, F 9, NF 10; nondominant side, NF 5; bilateral, F 1, NF 0; more than six months after tissue loss, F 10, NF 9; less than two months after tissue loss, F 5, NF 6; mean age, F 43.2 years, NF 40.6 years; mean years of education, F 12.1 years, NF 12.5 years; mean mass of tissue loss, F 66 gm., NF 66 gm.

TABLE 11.—*Wechsler-Bellevue Aggregate* *

Subjects	N	Age, Yr.	Schooling, Yr.	Impairment Score †		Performance I. Q.	
				Mean	S. D.	Mean	S. D.
Small frontal	9	45.2	11.1	8.00	8.64	94.89	14.94
Large frontal	12	42.5	11.9	12.83	11.30	94.83	13.17
Small nonfrontal	14	35.3	11.6	11.36	8.89	95.64	10.95
Large nonfrontal	10	46.0	10.8	26.40	13.89	73.80	13.30
All frontal	21	43.7	11.6	10.76	10.52	94.85	13.95
All nonfrontal	24	39.8	11.3	17.62	13.47	86.54	16.11
All small	23	39.2	11.5	10.04	8.95	93.35	12.66
All large	22	49.1	11.4	19.00	14.25	85.27	16.87
All subjects	45	41.6	11.4	14.42	12.66	90.42	15.70

Analysis of Variance for the Performance I. Q.

Source	*d. f.*	Sum of Squares	Mean of Squares	*F*
Site	1	774.4479	774.4479	4.21 ‡
Mass	1	1,141.3967	1,141.3967	6.21 ‡
Interaction	1	1,641.7633	1,641.7633	8.93 §
Error	42	7,537.3700	183.8383	
Total	45	11,094.9779		

* All subtest scores were expressed in terms of scores weighted in such a way that a large intact adult population will have a mean of 10.0 and a standard deviation of 3.0. (Wechsler, D.: *Manual for the Wechsler Adult Intelligence Scale*, New York, The Psychological Corporation, 1955). The *F* ratios for mass and site are significant at the 5% level, and the *F* ratio for interaction is significant at the 1% level. Consideration of the means and of the correlations with lesion mass indicates that, whereas the performances of the "small nonfrontal" and the "small frontal" groups were similar, the performance of the subjects with large nonfrontal lesions was much poorer than that of subjects with the large frontal lesions.

† Verbal I. Q. = Performance I. Q.

‡ Significant at 5% level.

§ Significant at 1% level.

through 5-18 opportunities for lever selections.

Three subjects had lesions, measuring 90-120 gm. Of these three subjects, all evidenced perseveration and Stage 3 reduced activity responses, which were prolonged and lasted through 19-39 opportunities for lever selections (Stage 4 immobility response).

Those seven subjects with the largest, or *E*, lesions (120-150 gm. or more) all perseverated and, in four out of seven instances, demonstrated Stages 3 and 4 reduced activity and immobility responses. One subject showed a Stage 4 response of complete immobility lasting 15 minutes.

The performance of those with lesions in the frontal lobes was similar to that of subjects with lesions in the nonfrontal regions with loss of similar mass of tissue.

Comment

In general, therefore, impairment was independent of site or side of the defect in the cerebral hemispheres but was directly related to the mass of hemisphere tissue loss. No one of the categories of highest functions was significantly or predictably impaired in relation to the site of defect, whereas all functions were progressively impaired with increasing mass of defect. The site of tissue loss, aside from its influence on the mass of the lesion and its effects on lower functions (such as speech mechanisms, simple sensation, and simple motility), did not determine the nature or the quantity of the impairment (Fig. 21).

Subjects with defects of a given mass showed significant individual differences in degree of dysfunction. It was possible to identify several major factors that contributed to this variation. Consideration of the premorbid history indicated that a major portion of this variation was related to premorbid adaptive capacity. Patients with a history of long periods of inadequate adjustment and severe mood disturbances, as well as those who reacted to evidence of their own impairment with great anxiety, exhibited greater impairment than did those with a more adequate premorbid adjust-

ment. Also, persons with a defect of a given mass who previously had demonstrated exceptional capacity (schooling, technical skill, positions of responsibility) were able to effect better adjustment and displayed less severe defects following brain loss than did the average subject with a defect of the same mass. These individual differences were less apparent when the mass of tissue was large. Thus, in addition to the factor of mass of tissue lost, it was also ascertained that the following factors were determinants of capacity following loss of tissue from the cerebral hemispheres of the neopallium: (*a*) the experience in, level of achievement in, and continued participation in scholarly, technical, cultural, and social activity; (*b*) the adequacy of the previous adjustment and evidence of prolonged inadequate adaptation and mood disturbances; (*c*) the dominant features of the prevailing premorbid defensive and compensatory reactions; (*d*) the environmental pressures (social, vocational, interpersonal, etc.) experienced during the period of progressive damage and thereafter, and (*e*) the rate of hemispheric damage, patients in whom destruction had been rapid being relatively more impaired. When the performance of otherwise comparable subjects with various (15 to 150 gm.) amounts of tissue removed from the neopallium were compared, a curve plotted from the data approximated a straight line in the limits defined. Numerous subjects with small lesions had proportionately greater impairment mass for mass than this straight-line relationship would indicate (Fig. 7). Those with small lesions,

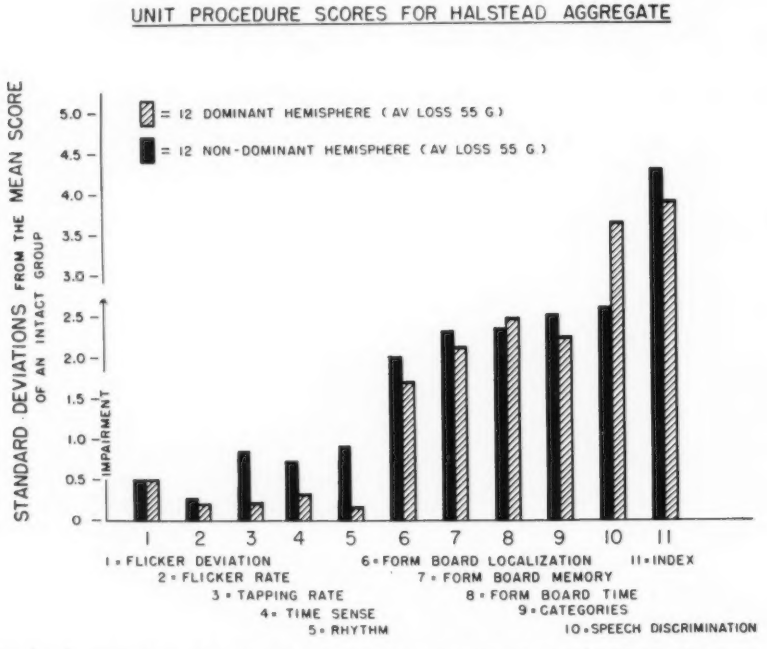

Fig. 5.—Average (mean) scores of the individual components of the Halstead Aggregate for 12 subjects with loss of tissue from the dominant hemisphere compared with the average scores for 12 subjects with loss of tissue from the nondominant hemispheres. Scores are expressed as deviations from the mean of intact (control) scores (in units of the standard deviation of the intact scores for that procedure). The two groups are matched in terms of average age, average years of education, etc.: number of subjects, D (dominant side) 12, N (nondominant side) 12; more than six months after tissue loss, D 9, N 10; less than two months after tissue loss, D 3, N 2; mean age, D 42.7 years, N 40.9 years; mean years of education, D 12.5, N 12.2; mean mass of tissue loss, D 55 gm., N 55 gm.

TABLE 12.—*Summary of Analysis of Variance (F Ratios) for the Components of the Wechsler-Bellevue Aggregate* *

	Over-All	Site	Mass	Interaction
1. Information	1	1	1	1
2. Comprehension	1.34	1	1	3.25
3. Arithmetic	2.59	1.61	1	5.82 †
4. Similarities	1	1	1	2.79
5. Digit span	1	1	1	1
6. Vocabulary	1	1	1	2.49
7. Digit symbol	3.95 †	1	7.67 ‡	3.91
8. Picture completion	1.89	1	1	4.78 †
9. Block design	10.53 ‡	5.18	8.23 ‡	18.17 ‡
10. Picture arrangement	4.44 ‡	1.82	6.19 †	5.31 †
11. Object assembly	4.32 ‡	3.03	6.05 †	3.89
12. Verbal I. Q.	1	1	1	1.48
13. Performance I. Q.	6.45	4.21 †	6.21	8.93 ‡
14. Full-scale I. Q.	1.73	1	1.03	3.53

Means, Standard Deviations, and Correlations (r) with Lesion Mass

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Small frontal														
Mean	10.0	9.11	9.11	8.56	8.67	9.00	6.67	8.11	7.67	8.22	8.44	99.44	94.89	97.11
S. D.	2.49	3.38	2.68	3.13	2.54	2.36	2.58	3.24	2.86	1.99	3.95	14.50	14.94	13.78
Large frontal														
Mean	10.67	11.25	11.91	10.67	8.83	11.83	6.00	9.58	8.33	7.75	7.25	106.91	94.83	100.50
S. D.	3.88	3.60	2.84	3.81	3.53	4.70	2.55	2.66	1.97	3.44	3.37	19.91	13.17	15.93
All frontals														
Mean	10.38	10.33	10.71	9.76	8.76	10.62	6.29	8.95	8.05	7.95	7.76	103.71	94.86	99.05
S. D.	3.37	3.67	3.10	3.69	3.15	4.12	2.58	3.01	2.42	2.92	3.68	18.17	13.96	15.14
r	0.105	0.269	0.399	0.183	—0.034	0.269	—0.229	0.255	0.034	—0.191	—0.233	0.188	—0.084	0.084
Small nonfrontals														
Mean	10.29	11.92	10.29	10.42	9.86	11.21	7.50	9.07	8.50	8.43	7.79	105.36	95.64	100.86
S. D.	2.93	3.71	3.13	2.58	4.18	3.38	2.26	2.63	1.84	2.32	3.19	15.67	10.94	13.76
Large nonfrontal														
Mean	11.10	10.30	8.50	9.30	7.80	10.20	3.90	7.00	3.70	4.70	3.40	100.20	73.80	88.10
S. D.	2.59	2.00	3.07	2.65	3.12	4.49	2.51	1.73	2.10	2.00	2.73	13.96	13.30	12.78
All nonfrontals														
Mean	10.62	11.25	9.54	9.96	9.00	10.79	6.00	8.20	6.50	6.87	5.96	103.20	86.54	95.54
S. D.	2.82	3.21	3.22	2.67	3.92	3.91	2.96	2.52	3.07	2.80	3.70	15.19	16.11	14.77
r	—0.072	—0.243	—0.432	—0.319	—0.235	—0.269	—0.702	—0.527	—0.776	—0.689	—0.570	—0.244	—0.714	—0.509

TABLE 12.—*Summary of Analysis of Variance (F Ratios) for the Components of the Wechsler-Bellevue Aggregate**—Continued

	Means, Standard Deviations, and Correlations (r) with Lesion Mass													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
All subjects														
Mean	10.51	10.82	10.09	9.87	8.89	10.71	6.13	8.56	7.22	7.38	6.80	103.44	90.42	97.18
S. D.	3.10	3.47	3.22	3.19	3.58	4.01	2.79	2.78	2.88	2.94	3.80	16.65	15.70	15.04
r	0.015	0.601	0.015	−0.033	−0.147	0.002	−0.455	−0.069	−0.331	−0.381	−0.330	−0.005	−0.337	−0.178

* The F ratios for site were significant for block design and for the impairment I. Q. at the 5% level; consideration of the mean indicates a greater impairment on these procedures in subjects with large nonfrontal lesions than in those with large frontal lesions. F ratios for mass were significant at the 1% level, for digit symbol, and for block design and were significant at the 5% level for picture arrangement, object assembly, and the performance I. Q. The F ratio for the interaction between site and mass was significant at the 1% level for block design and the performance I. Q., and at the 5% level for arithmetic, picture arrangement, and picture completion for all of these, the interaction ratio reflecting poorer performance in the subjects with large nonfrontal lesions.

† Significant at 5% level.

‡ Significant at 1% level.

Fig. 6.—Reappraisal of the total impairment score (mean of the standard scores for the 10 components) of the University of Chicago series (Shure and Halstead, 1958) for the Halstead Aggregate as related to mass of tissue loss. Subjects with scores for less than 8 of the 10 components were excluded. Lesion mass was re-estimated and raw scores converted to standard scores, as described in the text. The impairment scores of subjects both with frontal and with nonfrontal lesions were greater for subjects with large lesions than for subjects with small lesions (correlation coefficient $=0.45$). This correlation would occur by chance fewer than 5 times in 100. No differences in impairment scores on the basis of site were apparent when the data were reexamined in this manner.

perceiving fully their lacks and their threatened state, experienced the greatest anxiety and demonstrated the maximum display of defensive patterns. It is suggested that the stress experienced by these subjects is relevant to the disproportionate impairment scores demonstrated.[147]

After large occipital, parietal, or temporal lobectomy, the changes that were observed in patients who had undergone incomplete frontal resections were also noted, including altered reactions to painful stimuli, hyperactivity, cyclic fluctuation of mood and activity, "irritability," ready fatigability, freedom from preoccupation with personal anxieties and conflicts, defects in planning and initiative, inability to sustain purposive effort for more than a brief period, memory deficits, and a slower rate of accomplishing tasks.

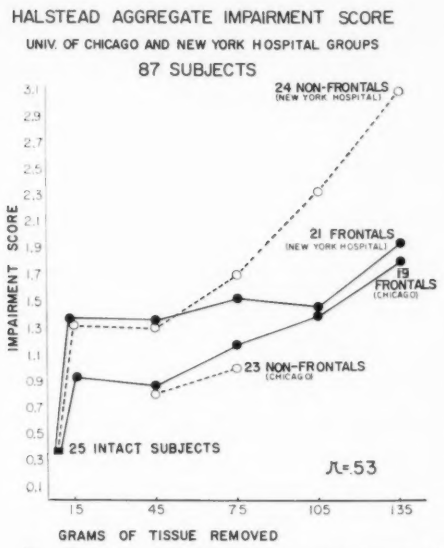

Fig. 7.—Mean total impairment scores (mean of standard scores for the 10 components of the Halstead Aggregate). The scores for the University of Chicago series were calculated from the data of Shure and Halstead, 1958. Subjects were excluded on whom less than 8 of the 10 components were reported, and the mass of tissue removed was re-estimated, as described in the text. It can be seen that, mass for mass, the performance of subjects with loss of tissue from the frontal lobes was similar to that of subjects with loss of tissue from nonfrontal regions for those with loss up to 60-90 gm. of tissue. Subjects with loss of tissue from nonfrontal regions larger than 60-90 gm. performed less well than did those with loss of similar mass from the frontal lobes; this greater impairment difference probably is a consequence of the major visual dysfunction in subjects with large nonfrontal defects. The over-all correlation of the individual impairment scores (87 subjects) with the mass of the lesion was 0.530. This correlation would occur by chance fewer than 1 time in 100. It is to be noted that, whereas the impairment scores for the New York Hospital series are similar to those of the University of Chicago series for subjects with a loss of more than 60-90 gm., the subjects of the Chicago series with lesions smaller than 60-90 gm. had lower impairment scores than did the subjects of the New York series, mass for mass. A straight line drawn from the point representing the performance of the subjects with loss of large amounts of tissue from the frontal lobes (who are free of the visual impairment present in the subjects with large nonfrontal lesions) to the mean "impairment score" calculated for 25 intact subjects (0.37) approximately describes the relationship of mass of tissue loss to degree of impairment. However, it can be seen that those with small lesions deviate from this straight-line relationship in the direction of being more impaired than would be predicted. This difference is more evident in the New York Hospital series. It was found that the subjects with small lesions perceived their threatened state fully and reacted to it with conspicuous display of adaptive and defensive mechanisms and much anxiety. On the other hand, perception of threat was impaired in those with large lesions, and anxiety was minimal. It is suggested that this reaction to threat in patients with smaller lesions accounts for the greater impairment of those with small lesions than would be expected from the straight-line relationship. The factor of reaction to threat would probably vary from series to series, depending upon educational, cultural, social, and economic factors.

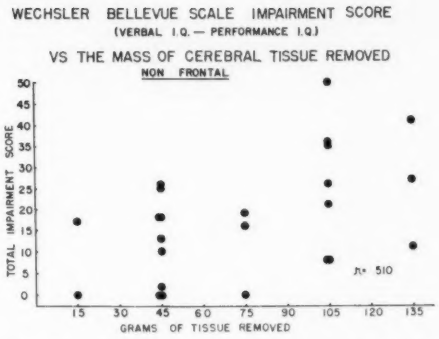
WECHSLER BELLEVUE SCALE IMPAIRMENT SCORE
(VERBAL I.Q. — PERFORMANCE I.Q.)
VS THE MASS OF CEREBRAL TISSUE REMOVED
NON FRONTAL
TOTAL IMPAIRMENT SCORE
R= 510
GRAMS OF TISSUE REMOVED

Fig. 8.—Total impairment scores (verbal I. Q.; performance I. Q.) on the Wechsler-Bellevue Aggregate for 24 subjects with lesions in the parietal, occipital, or temporal lobes as related to mass of tissue loss. The correlation coefficient for the relationship between impairment score and mass of lesion was 0.51, a degree of correlation that would be expected to occur fewer than 5 times in 100 by chance.

An exception to the generalization that degree of impairment was relevant to mass regardless of site was observed in respect to higher visual function. When subjects were matched for mass of tissue loss, those with parietal, temporal, or occipital lobe loss performed relatively less well than did those with frontal lobe loss, although these subjects were also impaired. Poorly performed were assay procedures requiring rapid visual synthesis, visual imagery, or visual perception in the face of simultaneous and irrelevant visual stimuli (Figs. 4 and 11). Furthermore, in responding to the Rorschach Ink Blots, a procedure that implicates visual imagery and fantasy, the performance of subjects with lesions in the nonfrontal regions was more impaired mass for mass than was the performance of those with lesions in the frontal regions.

In these subjects who showed no perceptible aphasia, only slight differences in im-

TABLE 13.—*Rorschach Ink Blots* *

Subjects	*N*	Mean Age, Yr.	Mean Schooling, Yr.	Impairment Score	
				Mean	S. D.
Small frontal	6	44.1	10.3	14.83	10.35
Large frontal	8	40.5	12.0	24.25	12.71
Small nonfrontal	10	34.8	11.1	25.80	11.17
Large nonfrontal	7	48.7	11.4	34.43	14.91
All frontals	14	46.1	11.3	20.21	12.65
All nonfrontals	17	40.4	11.2	28.76	13.69
All small	16	39.6	10.8	21.06	11.89
All large	15	46.8	11.7	29.00	14.69
All subjects	31	43.1	11.3	24.90	13.89

Correlation of impairment score with mass of lesion: frontals 0.385; nonfrontals 0.517; all subjects 0.355

Analysis of Variance for the Impairment Score

Source	*d. f.*	Sum of Squares	Mean of Squares	*F* †
Site	1	561.2938	561.2938	3.20
Mass	1	487.7722	487.7722	3.14
Interaction	1	197.9961	197.9961	1.13
Error	27	4,739.6476	175.5925	
Total	30	5,986.7097		

* The impairment score for the responses to the Rorschach Ink Blot test was the sum of the individual ratings on the 28 criteria described in the text. The *F* ratios for mass and for site approached, but did not achieve, significance at the 5% level. The differences were in the direction of higher impairment scores for those with large (90-150 gm.) lesions and higher impairment scores for those with nonfrontal lesions. This trend toward greater impairment in the nonfrontal subjects was apparent both for thoses with small lesions and for those with large lesions.

† For significance at 5% level, $F=4.17$; at 1%, $F=7.56$.

TABLE 14.—*Mean Scores and Standard Deviations for the Twenty-Eight Configurational Criteria for Rating the Responses to the Rorschach Ink Blots*

Criterion	Small Frontal		Large Frontal		Small Nonfrontal		Large Nonfrontal	
	Mean	S. D.	Mean	S. D.	Mean	S. D.	Mean	S. D.
1	1.33	1.10	1.12	1.27	1.90	0.94	1.57	0.49
2	0.83	0.90	1.25	0.96	1.50	0.92	1.71	0.45
3	1.50	0.96	1.12	0.60	1.70	0.90	1.57	1.05
4	1.00	1.10	1.56	1.00	1.30	0.78	2.29	0.69
5	0.83	0.90	1.62	1.21	1.20	1.07	2.29	0.45
6	0.67	1.10	1.50	1.22	1.60	1.11	1.57	0.90
7	0.83	1.06	0.87	1.05	1.30	0.78	1.86	0.64
8	0.67	0.47	1.25	0.97	1.20	0.60	1.57	0.73
9	0.67	0.94	1.50	0.87	1.00	1.00	1.71	1.03
10	1.33	1.10	0.87	0.78	1.40	1.11	1.71	1.03
11	0.67	0.94	1.25	0.97	1.20	0.98	1.43	1.40
12	0.50	0.76	0.87	1.05	1.00	0.77	1.57	1.17
13	0.83	0.90	0.87	0.93	1.00	0.77	1.71	1.16
14	0.50	1.12	0.37	0.70	0.90	0.83	1.14	0.83
15	0.17	0.37	0.75	0.97	0.70	1.00	0.71	0.88
16	0.33	0.47	0.87	0.92	0.90	1.04	1.43	0.73
17	0.50	1.12	0.75	1.09	0.50	0.50	1.29	0.88
18	0.17	0.37	0.75	1.09	0.50	0.92	0.86	0.83
19	0.50	0.76	0.50	0.71	0.70	0.78	0.71	0.76
20	0.17	0.37	0.50	1.00	0.60	0.66	1.00	0.53
21	0.17	0.37	1.12	0.60	0.40	0.66	0.71	0.45
22	0.17	0.37	1.50	0.71	0.50	0.67	1.29	0.88
23	0.17	0.37	0.62	0.99	0.50	0.67	0.71	0.88
24	0.33	0.74	0.12	0.33	0.10	0.30	0.43	0.49
25	0.17	0.37	1.00	1.00	0.60	0.80	1.43	1.18
26	0.17	0.37	0.50	1.00	0.10	0.30	0.43	0.49
27	0.17	0.37	0.25	0.43	0.40	0.49	0.86	0.83
28	0.17	0.37	0.12	0.33	0.20	0.40	0.14	0.35

TABLE 15.—*Conditioned Reactions* *

Subjects	N	Age, Yr.	Schooling, Yr.	Impairment Score	
				Mean	S. D.
Small frontal	9	45.7	11.1	62.11	37.88
Large frontal	14	41.9	11.6	78.78	45.23
Small nonfrontal	13	40.2	11.1	59.38	25.82
Large nonfrontal	5	47.0	15.2	94.8	33.29
All frontal	23	43.34	11.4	72.26	43.28
All nonfrontal	18	42.1	12.2	69.22	32.26
All small	22	42.4	11.1	60.50	31.35
All large	19	43.2	12.6	83.00	43.00
All subjects	41	42.8	11.8	70.93	38.86

Correlation of impairment score with mass of lesion: frontals 0.355; nonfrontals 0.655; all subjects 0.432

Analysis of Variance for the Impairment Score

Source	d. f.	Sum of Squares	Mean of Squares	F †
Site	1	93.2346	93.2346	1
Mass	1	5,161.2805	5,161.2805	3.42
Interaction	1	891.1424	891.1424	1
Error	37	55,779.1230	1,507.5438	
Total	40	61,924.7805		

* The impairment score for the conditioned-reactions procedure was the sum of the number of trials required to achieve a stable response for components 1A, 2A, and 3A, described in the text.

The F ratio for site and interaction were not significant. The F ratio for mass approached, but did not achieve, significance at the 5% level. The difference was in the direction of poorer performance by those with large (90-150 gm.) lesions.

† For significance at 5% level, $F=4.085$; at 1% level, $F=7.31$.

pairment of the highest integrative functions were observed between those with loss in the dominant hemisphere and those with loss in the nondominant hemisphere, the latter showing somewhat less impairment. However, in specific test procedures most involving speech function (Figs. 5 and 12), those with lesions in the dominant hemisphere performed less well.

The elements of these highest functions were not equally fragile. An hierarchy of the various components could be discerned in terms of a ranking of the functions impaired as the mass of cerebral hemisphere tissue loss increased, regardless of site. Impairment of imagery, curiosity, pursuit of adventure, new experiences, speed of reaction, spontaneity, rapid learning, abstraction, and ability to resist the disorganizing

TABLE 16.—*Summary of Correlations of Impairment Scores with Mass of Tissue Loss*

Aggregate	Frontal	Nonfrontal	All Sites
Wechsler-Bellevue	0.307	0.510 *	0.331 †
Halstead (New York Hospital)	0.350	0.771 *	0.507 *
Halstead (Univ. of Chicago)	0.586 *	0.280	0.445 *
Halstead (pooled series)			0.530 *
Conditioning	0.355	0.655 *	0.432 *
Rorschach	0.380	0.517 †	0.355 †

* Significant at 1% level.
† Significant at 5% level.

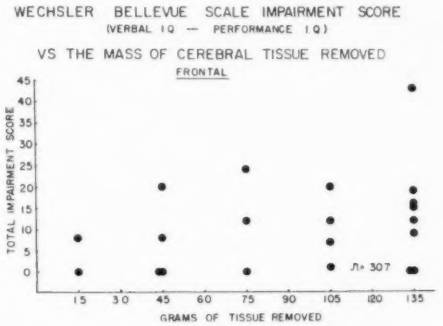

Fig. 9.—Total impairment scores (Verbal I. Q.; Performance I. Q.) on the Wechsler-Bellevue Aggregate for 21 subjects with lesions in the frontal lobes as related to mass of tissue loss. The correlation coefficient for the relationship between impairment score and mass of lesion was 0.31, a degree of correlation that would be expected to occur oftener than 5 times in 100 by chance.

effects of stress was evident in subjects with small lesions (A and B class), whereas vocabulary, long-utilized skills, and factual information were not significantly impaired until there was a much greater tissue loss.

The largest hemispheric defects were associated with the highest impairment scores and the most striking alterations in behavior. Such large defects occurred most frequently in the frontal lobes. Defects of comparable size within Classes A, B, and C resulted in similar impairment scores, as seen both in laboratory procedures and in the broader life situation, regardless of whether such defects were in the frontal lobes or elsewhere in the cerebral hemispheres (Fig. 19). However, subjects with large nonfrontal lesions (Class D and E) performed less well than did those with similarly large lesions in the frontal lobe. It was inferred that this greater impairment stemmed from defects in visual function in these subjects.

II. Studies of Performance of Subjects with Diffuse Loss of Brain Substance

In 1954, Engeset and Lönnum[150] indicated that a relatively close relationship existed between the degree of impairment of highest-level functions and the extent of cerebral atrophy as measured by the width of the third ventricle in standard pneumoencephalographic views. Evidence based on subjects with diffuse atrophy is of less value for assessing the relationship between the highest integrative functions and the loss of brain mass than are the data collected from subjects with measured focal loss of tissue, since in the latter the remaining brain tissue is not involved in progressive disease. In-

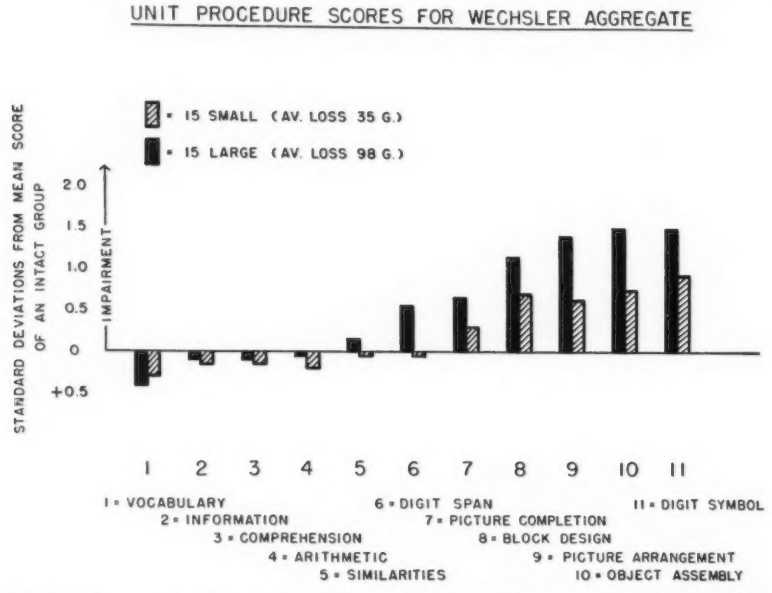

Fig. 10.—Average (mean) scores of the individual components of the Wechsler-Bellevue Aggregate for 15 subjects with loss of small (less than 60 gm.) amounts of cerebral hemisphere tissue compared with the average scores of 15 subjects with loss of large (60-150 gm.) amounts of tissue. Scores are expressed as deviations from the mean of intact (control) scores (in units of the standard deviation of the intact scores for that procedure). The two groups are matched in terms of average age, average years of education, etc.: number of subjects, S (small) 15, L (large) 15; dominant side, S 9, L 9; nondominant side, S 6, L 4; bilateral, S 0, L 2; more than six months after tissue loss, S 12, L 11; less than two months after tissue loss, S 3, L 4; mean age, S 42.0, L 42.8; mean years of education, S 11.6, L 11.8; mean mass of tissue loss, S 35 gm., L 98 gm.; frontal lobe site, S 6, L 7; nonfrontal site, S 9, L 8.

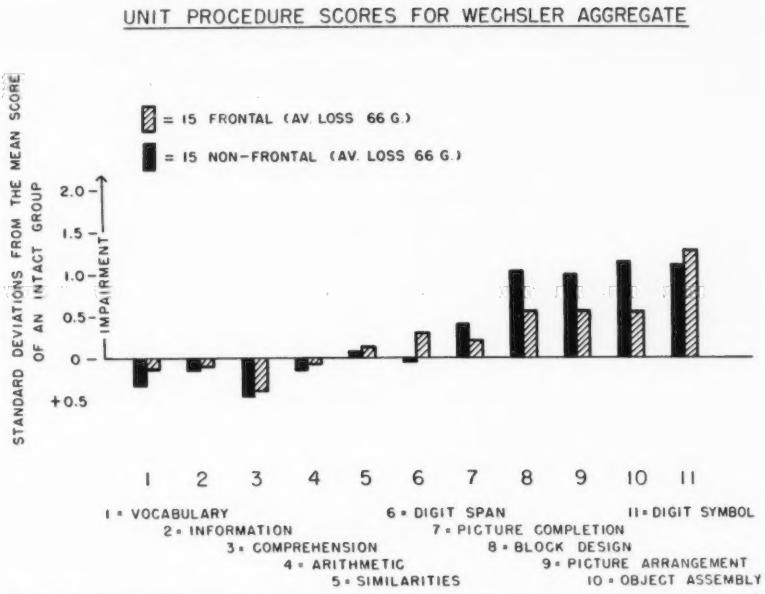

Fig. 11.—Average (mean) scores of the individual components of the Wechsler-Bellevue Aggregate for 15 subjects with loss of cerebral hemisphere tissue from the frontal lobes compared with the average scores for 15 subjects with loss of tissue from the parietal, temporal, or occipital lobe. Scores are expressed as deviations from the mean of intact (control) scores (in units of the standard deviation of the intact scores for that procedure). The two groups are matched in terms of average age, average years of education, etc.: number of subjects, F 5, NF (nonfrontal) 15; dominant side, F 9, NF 10; nondominant side, F 5, NF 5; bilateral, F 1, NF 0; more than six months after tissue loss, F 10, NF 9, less than two months after tissue loss, F 5, NF 6; mean age, F 42.2 years, NF 40.6 years; mean years of education F 12.1, NF 12.5; mean mass tissue loss F 66 gm., NF 66 gm.

deed, patients with atrophy in most instances have progressive degenerative disease of the brain, hence, much of the surviving tissue is not functioning properly. Hence, pneumoencephalographic evidence of tissue loss in patients with cerebral atrophy gives only a gross indication of the total amount of defective tissue of the hemispheres. Furthermore, those patients whose performance deteriorated rapidly as an aspect of degenerative disease of the hemispheres often showed less atrophy in the earlier phases of the process than did those patients who had a more slowly progressive disease (and a similar degree of deterioration of performance). Recognition of this fact has lead to a selection of those patients for study who had shown evidence of slow deterioration of highest-level functions over a period of several years.*

The 20 adult subjects selected for study all had had pneumoencephalographic studies performed after a relatively recent period of poor performance at home or at work or after a seizure. The nature of the process responsible for the cerebral atrophy was not definable by the methods used. In all subjects it was slowly progressive and generally met the clinical criteria for "presenile" degeneration. The process involved much of the hemispheres more or less symmetrically and apparently included all lobes. The subjects did not exhibit striking defects in motility or sensory functions. Convulsions had occurred in only two patients and totaled three in all. The spinal

* Data for this section were gathered in association with Ari Kieve, M.D. They have been reported separately in summary,[180] and a more detailed presentation is in preparation.

fluid was free of cells and signs of infection, although the protein content was raised in a few (to 89 mg/100 cc.), and, when tested, a few of the specimens contained abnormal amounts of protease and polypeptides. Vascular disease was probably present in some patients, but signs of focal degeneration and hemorrhage were absent.

In addition, the subjects with atrophy of the cerebral hemispheres studied (*a*) did not have conspicuous deficits of speech or language, (*b*) were not more than 60 or less than 30 years of age, (*c*) did not have a history or evidence of increased intracranial pressure, (*d*) did not have surgical resection of tissue from the cerebral hemispheres, and (*e*) did not have brain tumors, chronic alcoholism, drug addiction, or significant abnormalities other than those under study.

As with the subjects with focal defects, these subjects were studied in their natural setting and in the laboratory.

Studies included (1) interviews with subjects in regard to behavior, attitudes, performance, and thinking processes; (2) reports of the subjects' behavior, utterances, and performance by their families, friends, and employers (from this information the subjects' biography and current environment were ascertained, and inferences were drawn concerning over-all adaptive capacity, as contrasted with their premorbid state); (3) the conditioning procedures previously described, and (4), in addition, the procedures to assess the capacity to withstand repetitive failure previously described.

To establish base-line scores for the conditioning procedures, 50 subjects with intact cerebral hemispheres were studied.

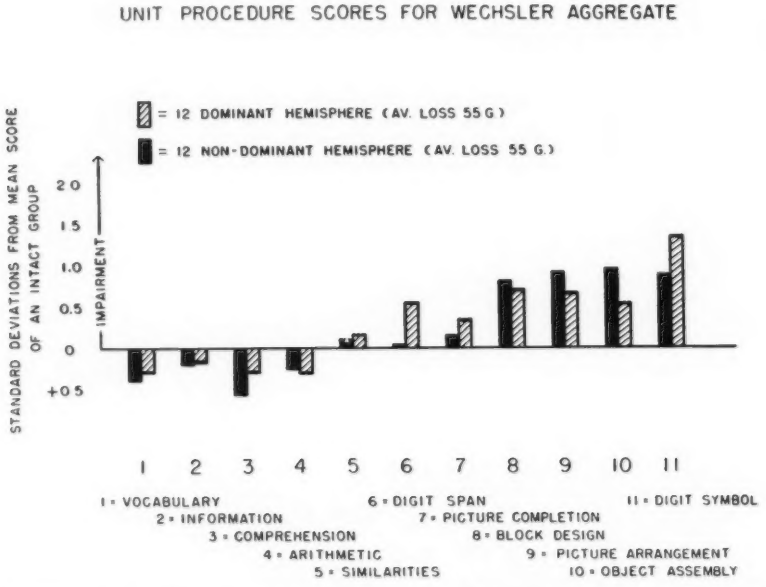

Fig. 12.—Average (mean) scores of the individual components of the Wechsler-Bellevue Aggregate for 12 subjects with loss of tissue from the dominant hemisphere, as compared with the average scores of 12 subjects with loss of tissue from the nondominant hemispheres. Scores are expressed as deviations from the mean of intact (control) scores (in units of the standard deviation of the intact scores for that procedure). The two groups are matched in terms of average age, average years of education, etc.: number of subjects, D (dominant side) 12, N (nondominant side) 12; more than six months after tissue loss, D 9, N 10, less than two months after tissue loss, D 3, N 2; mean age, D 42.7, N 40.9; mean years of education, D 12.5, N 12.2; mean mass of tissue loss, D 55 gm., N 55 gm.

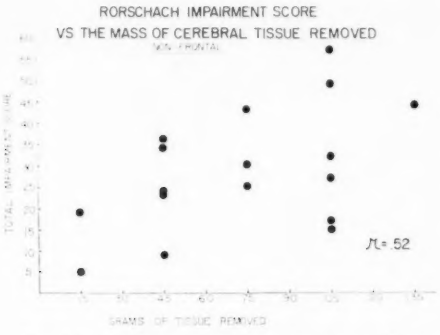

Fig. 13.—Total impairment scores (sum of ratings from 0 to 3 for the 28 configurational categories described in the text) for the responses to the Rorschach Ink Blots of 17 subjects with lesions in the parietal, occipital, or temporal lobe as related to mass of tissue loss. The correlation coefficient for the relationship between impairment score and lesion mass was 0.52, a degree of correlation that would be expected to occur fewer than 5 times in 100 by chance.

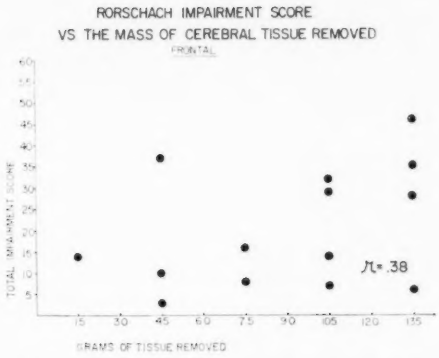

Fig. 14.—Total impairment scores (sum of the ratings from 0 to 3 for the 28 configurational categories described in the text) for the responses to the Rorschach Ink Blots of 14 subjects with lesions in the frontal lobes as related to mass of tissue loss. The correlation coefficient for the relationship between mass of lesion and impairment score was 0.38, a degree of correlation that would be expected to occur oftener than 5 times in 100 by chance.

Forty pneumoencephalograms of subjects in whom no demonstrable disease process was present were measured to establish base-line scores for the normal pneumoencephalograms.

The extent of tissue loss was estimated by measuring the area occupied by the air in the lateral ventricles, as seen in the technically satisfactory pneumoencephalograms. Specifically, the right and left lateral views were studied and measured. The lower border of the intracranial area representing total mass of hemispheres was established by drawing a line from the external occipital

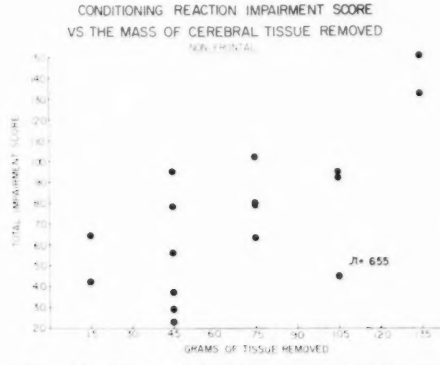

Fig. 15.—The total impairment scores (the sum of the number of trials required to establish several conditioned responses, Steps 1, 2, and 3 as described in the text) on the conditioned response procedure for 17 subjects with lesions in the parietal, occipital, and/or temporal lobes as related to mass of tissue loss. The correlation coefficient for the relationship between impairment scores and mass of lesion was 0.65, a degree of correlation that would be expected to occur fewer than 1 time in 100 by chance.

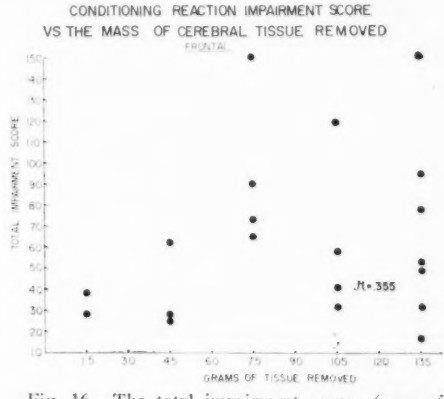

Fig. 16.—The total impairment scores (sum of the number of trials required to establish and to extinguish several conditioned responses, Steps 1, 2, and 3 as described in the text) on the conditioned response procedure for 20 subjects with lesions in the frontal lobes as related to mass of tissue loss. The correlation coefficient for the relationship between impairment score and mass of lesion was 0.35, a degree of correlation that would be expected to occur oftener than 5 times in 100 by chance.

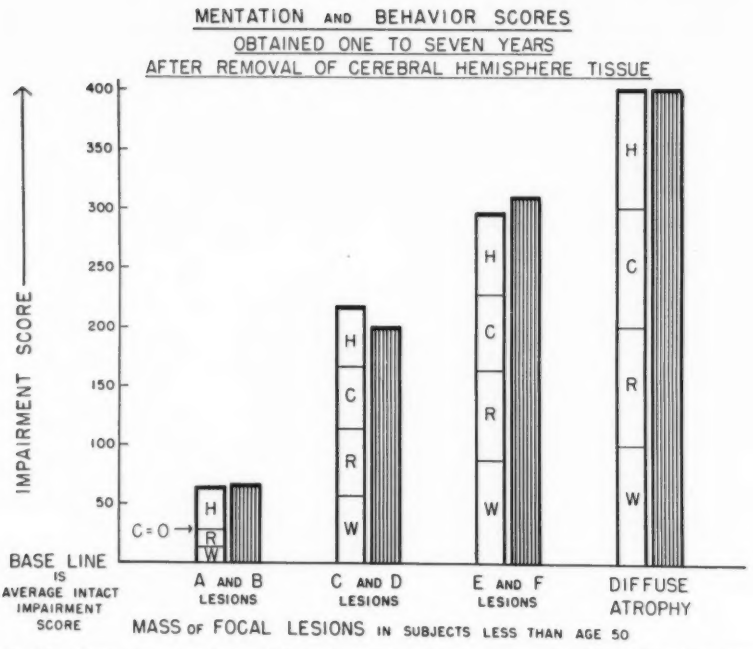

Fig. 17.—Over-all mentation and behavior scores for a group of subjects less than age 50, obtained one to seven years after removal of cerebral hemisphere tissue, demonstrating that the degree of impairment of highest integrative functions increases as the mass of the tissue loss increases. Impairment was measured by both laboratory and extralaboratory criteria. The latter is indicated by the vertically lined columns, and the laboratory criteria, by the hollow blocks: *H*, Halstead aggregate; *C*, conditioned reactions; *R*, Rorschach; *W*, Wechsler-Bellevue aggregate. Note that the impairment scores obtained from laboratory and extralaboratory criteria approximate each other. *A*, lesions representing mass up to 30 gm.; *B*, lesions, mass from 30 to 60 gm.; *C*, lesions, mass from 60 to 90 gm.; *D*, lesions, mass from 90 to 120 gm.; *E*, lesions, mass from 120 to 150 gm.; *F*, lesions, mass, from 150 to 180 gm. Diffuse atrophy was moderate in degree and was verified by x-ray studies or by visualization at craniotomy.

protuberance to the most anterior portion of the floor of the anterior fossa. The inner table of the cranium outlined the remaining borders. A lateral view was placed against an x-ray viewing box and overlaid with graph paper ruled in small squares. The outline of the lateral ventricles and that of the total intracranial area in each view were traced onto the ruled paper. The area occupied by each ventricle and each hemisphere, as defined, was expressed in terms of the number of ruled squares in the traced area. The ratio of the sum of the area occupied by the two ventricles to the sum of the area occupied by the two hemispheres was referred to as the ventricle-hemisphere ratio. Thus, in the intact subject, the average ventricle-hemisphere ratio was 1:11, or 0.09, with a range from 0.05 to 0.14. In contrast, in subjects with the greatest loss of cerebral substance, there was a greater amount of air in the ventricles, and relatively less hemispheric substance, and in these subjects the ventricle-hemisphere ratio was 1:3, or 0.34.

It was found that subjects with demonstrable loss of tissue from the cerebral hemispheres had greater difficulty than intact subjects in establishing conditioned responses. Thus with progressively larger amounts of tissue loss from the cerebral hemispheres, as defined by the ventricle-hemisphere ratio, the subjects required increasing numbers of trials to establish stable

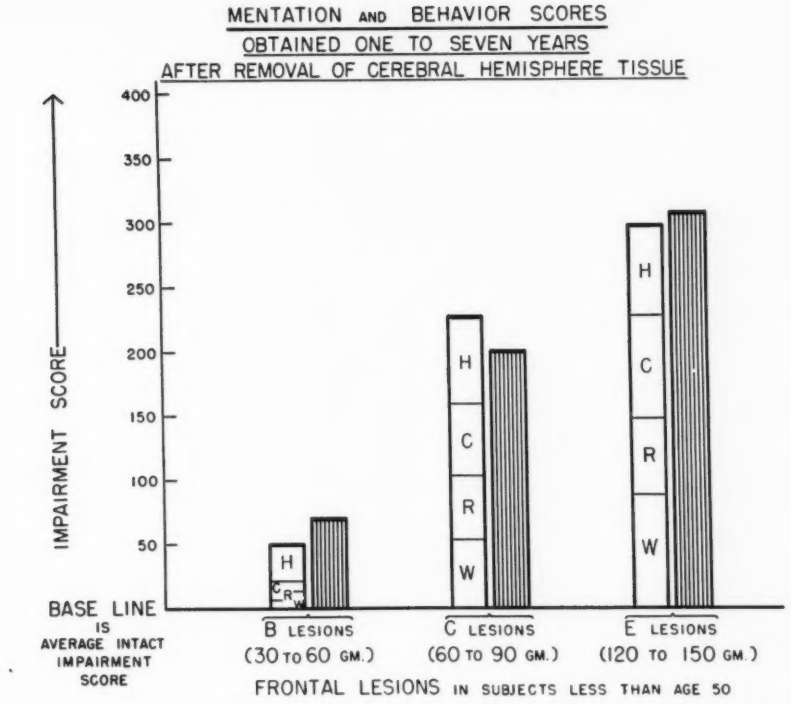

Fig. 18.—Over-all mentation and behavior scores obtained one to seven years after removal of cerebral hemisphere tissue, demonstrating that the degree of impairment of highest integrative functions increases with increasing mass of tissue loss in subjects in whom the loss of cerebral hemisphere tissue was limited to the frontal lobes.

conditioned reactions. While the subjects with tissue loss had difficulty in establishing simple conditioned responses, they had even greater difficulty in establishing differential conditioned responses. This difficulty was striking when a positive conditioned stimulus was presented after a negative conditioned stimulus within the same sensory modality (i. e., tone). Conspicuous difficulty was experienced by those with tissue loss when they attempted to establish a positively conditioned response to a tone if that tone followed three previously conditioned inhibitory stimuli (i. e., two tones and a light).

Although patients with no atrophy or with mild atrophy improved in performance as they proceeded with the conditioning procedures from 1A to 1E (see "Method"), no comparable improvement was attained by subjects with severe loss and only slight improvement by those with moderate loss.

In Step 2, i. e., with further experience, performance in all groups improved. However, the greater the loss of tissue the less improvement was noted, particularly in the differential conditioning procedures. When the first conditioned stimulus was again presented after Step 2, the intact subjects performed well, whereas those with measurable amounts of tissue loss required more trials, despite the fact that they had previously become conditioned to these particular stimuli.

Subjects finally were exposed to a period during which shock accompanied each stimulus regardless of response, at which time all positive and negative conditioned stimuli used previously were presented. After this

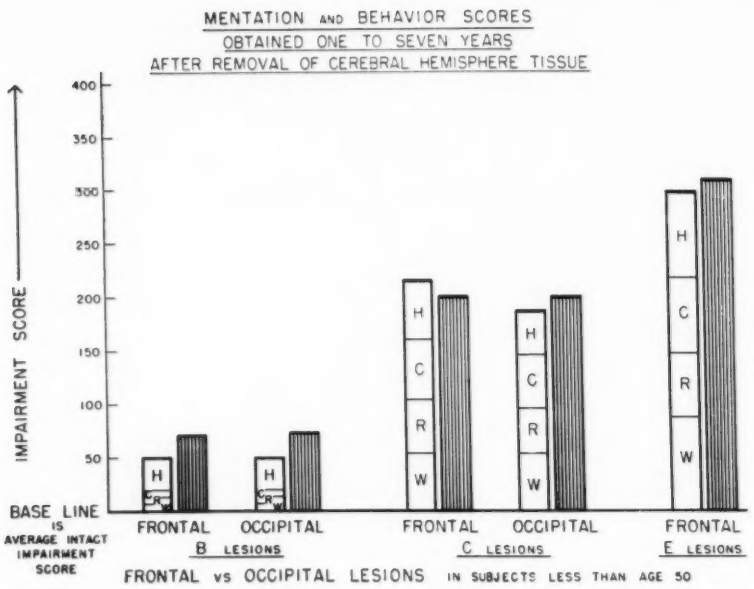

Fig. 19.—Over-all mentation and behavior scores for a group of subjects, aged less than 50, obtained one to seven years after removal of cerebral hemisphere tissue, demonstrating that the loss of Class *B* and *C* amounts of cerebral hemisphere tissue is accompanied by similar degrees of impairment whether the tissue loss is from the frontal or from the occipital lobes. Subjects with Class *E* lesions, which occur most frequently in the frontal lobes, are more impaired than subjects with smaller loss of tissue, whether it be from the frontal or from the occipital lobes.

period they were permitted to reestablish the previous conditioned response by again reenforcing the desired response. Again, the ability to recover the conditioned response previously established after such a period of "frustration and failure" was most deficient in those with large amounts of tissue loss from cerebral hemispheres.

The performance of these subjects with diffuse cerebral atrophy is compared with that of subjects with focal defects in Figure 22. A review of the subjects' biographical data and interviews with the subjects and their families permitted the evaluation of the degree of impairment in over-all adaptive capacity in the setting of their daily lives. Each subject was evaluated in terms of his capacity for the expression of needs, appetites, and drives; the capacity to employ effectively the mechanism for goal achievement (perception, learning, memory, etc.); the capacity to maintain appropriate thresholds and tolerance for frustration and anxiety and to recover rapidly from their effects, and the capacity to maintain effective and well-modulated defense reactions. Each was then assigned a cumulative score, which designated the degree of impairment of over-all adaptive capacity.

The amount of loss of tissue from the hemispheres was seen to be related roughly to the degree of impairment of over-all capacity; i. e., subjects with large amounts of cerebral hemispheric damage were most impaired in their social and interpersonal adjustment. Similarly, the degree of such impairment was again roughly related to performance during laboratory conditioning procedures.

A review of the histories and the data from interviews of the patients and their families established that certain features of impairment of the highest integrative functions were predictably present in the various groups studied. Despite the individual differences linked with premorbid experience

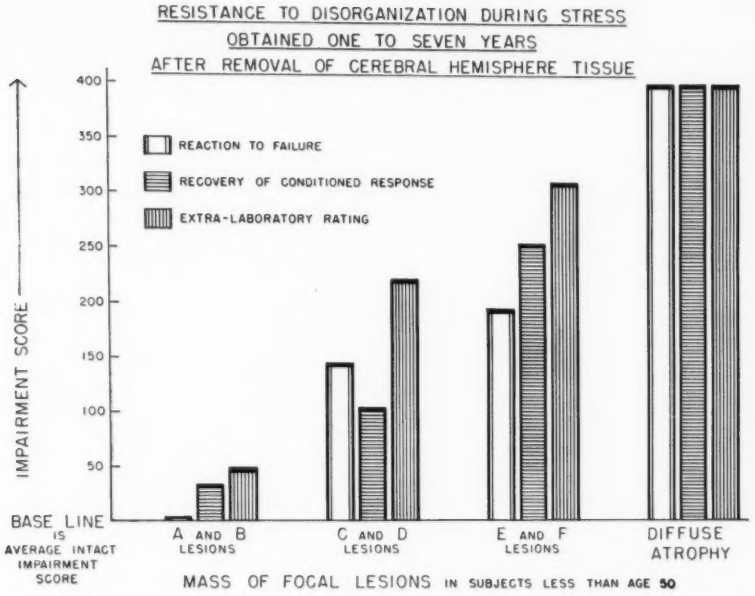

Fig. 20.—Demonstration in subjects less than age 50, that impairment of resistance to disorganization during stress increased with increased mass of cerebral hemisphere tissue loss. These impairment scores were obtained one to seven years after removal of cerebral hemisphere tissue. The "reaction to failure" procedure is described in the text. The "recovery of conditioned response" score is based on the number of trials required to reestablish a previously stable conditioned response after a period of induced failure. The "extralaboratory rating" was based on two of the extralaboratory criteria listed in Table 1, i.e., (1) reduction of the thresholds for deprivation and frustration and (2) longer-lasting and severer disorganization after frustration, deprivation, failure, or conflict.

and the adequacy of premorbid adjustment, these features were related to the degree of tissue loss, varying from mild to severe. Thus, various stages of decline with increasing loss of substance from the cerebral hemispheres could be defined. The degree of impairment in over-all adaptive capacity outside the laboratory of those with slight atrophy as defined was roughly equivalent to that observed in subjects with focal removal of up to 90 gm. of tissue from the cerebral hemispheres. Those with moderate atrophy exhibited impairment equivalent to that observed in subjects with focal removal of 90-120 gm. Those with severe diffuse loss of tissue exhibited impairment which was usually worse than that scored by subjects with focal lesions of 120-150 gm. or more.

Slight Diffuse Loss of Tissue from the Cerebral Hemispheres

(Ventricle-Hemisphere Ratio 0.11:0.16)

These patients continued to work, but showed lessened ambition, initiative, or imagination. They attempted to deal with daily problems by constricting the fields of interest and habitually performing old routinized patterns, at work, at home, and in the community. Defense reactions were integrated less well and were modulated poorly, although the subjects often maintained relatively effective states for long periods by repeating old, previously learned patterns. Disinterested, detached behavior and the capacity to participate fell off concurrently. Several remained at home a good part of the day, staring into space, rarely seeking the company of others or the ad-

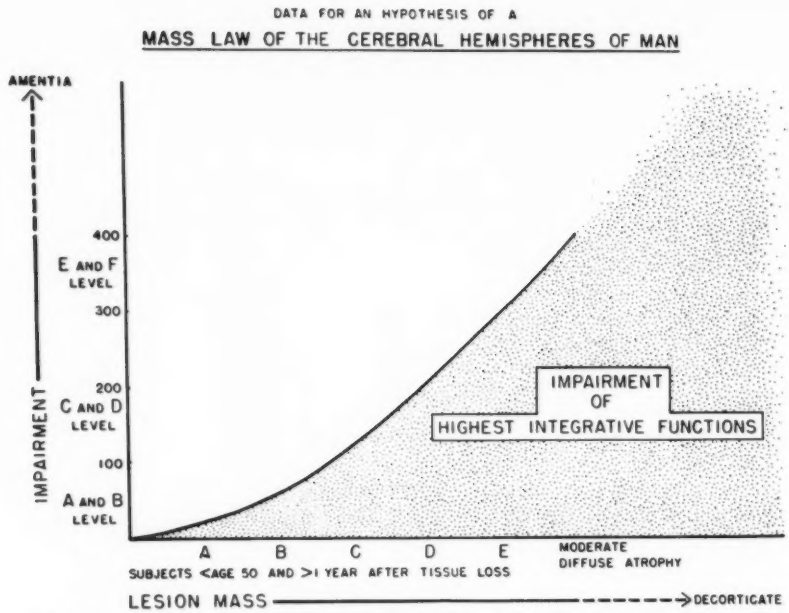

Fig. 21.—Graphic presentation of data for an hypothesis of a mass law of the cerebral hemispheres of man, showing a progressive increase of impairment of higher integrative functions with increasing loss of hemisphere tissue. Impairment is based on performance on four blocks of laboratory procedures (Wechsler-Bellevue Aggregate, Halstead Aggregate, Rorschach, and conditioned reactions.)

vantages of the community's entertainment facilities. Social responsibility was avoided, and athletic endeavors were diminished or absent. Recall was delayed; calculation was labored, and persistent effort was increasingly difficult. Frustration threshold and tolerance were lowered, and the subjects were irritable or showed outbursts of hos-

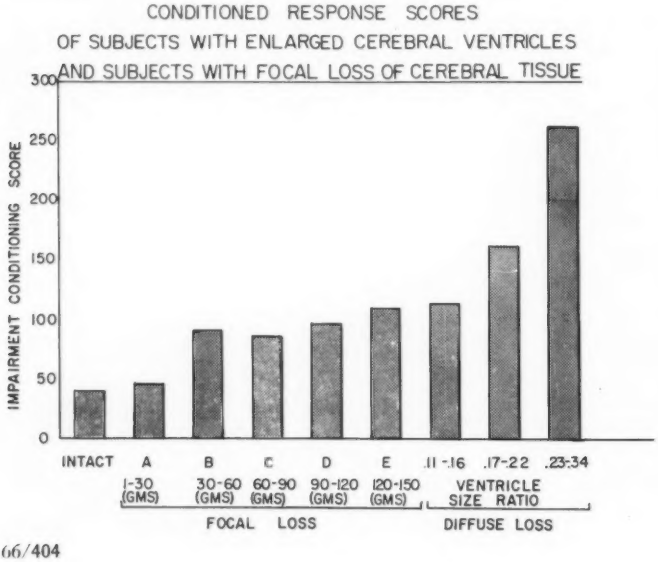

Fig. 22.—Mean total impairment scores (sum of the number of trials required to establish and to extinguish several conditioned responses, Steps 1, 2, and 3 as described in the text) on the conditioned response procedure for subjects with diffuse loss of tissue from the cerebral hemispheres as demonstrated by enlargement of lateral ventricles in the pneumoencephalogram. The mean scores of subjects with focal loss of from 15 to 150 gm. of tissue from the cerebral hemispheres is presented for comparison.

tility. Situations which were new, which might lead to failures, or which required decision making or incisive action were avoided. Anxiety was sometimes conspicuous. The expression of affect often appeared inappropriate, and there was a paucity of expression of feeling. Examination of the patient revealed impairment in memory in regard to recent events, slowed calculation, and poorly performed serial 7's tests, but no significant loss in vocabulary or general information.

Moderate Diffuse Loss of Tissue from the Cerebral Hemispheres

(Ventricle-Hemisphere Ratio 0.17:0.22)

These patients experienced great difficulty in family, social, and occupational situations, in performance of duties and responsibilities, and in their interpersonal relationships. Often their dress was inappropriate, and they were careless about bodily cleanliness. Activities were slowed and required more effort. Performance on the job was characterized by increasing errors, decreased productivity, and difficulty with following directions, and planning became impossible. Memory for the recent past was frequently significantly impaired. Many were circumstantial about the past, losing the thread of an account and relating irrelevant details at length. Anxiety was minimal. Their affect was frequently inappropriate or bland or conveyed little warmth. Conversation dealing with abstract topics was almost impossible. Their statements dealing with abstractions often were illogical, distorted, and frequently contradictory. The premorbid defensive reactions were in general diminished and they were so poorly controlled, transparent, splintered, and "silly" that they often led to socially unacceptable behavior. The expressions of appetites and drives, though not strong, were often inappropriately exhibited: Restlessness and overactivity were features of the behavior of some, but, again, extreme fatigability and exhaustion were commoner. Testing revealed memory impairment, calculation difficulties, inability to perform or persist with serial 7's, inability to comprehend aphorisms and metaphor, and defects in conceptual ability, insight, and judgment.

Severe Diffuse Loss of Tissue from Cerebral Hemispheres

(Ventricle-Hemisphere Ratio 0.23:0.34)

The patients were considered to be seriously demented by their families and friends. They were untidy and lacking in a show of interest in their environment. Orientation was deficient in all spheres, especially in regard to time. Identification of body parts was performed poorly; right and left differentiation sometimes was impossible. Vocabulary was deficient and early factual information was retained only in part. Abstractions and conceptual ability were markedly deficient. Remote and recent memory was impaired. Calculation was grossly deficient. Retention was poor. Judgment and insight into personal problems were grossly defective. Frequently the patients were unable to perform previously learned skilled acts, or even simple motor acts. There was frequently perseveration of phrases, particularly in situations regarded by the subjects as threatening. Many of these patients were "obtunded." When requested to keep their eyes closed, they opened them after only a brief interval. Grasp reflexes in hands and feet could be demonstrated in some. They were unconcerned about personal hygiene, appearance, exercise, and nutrition. All required supervision and most custodial care. Perceptions of all sorts were reduced, slowed, and distorted. There was little show of interest in food, bodily warmth, and preservation of self and kin. Their affect was bland, and most of the time they were apathetic. Anxiety was minimal, and defensive and compensatory reactions no longer were maintained. Failure or frustration led rapidly to further disorganization of their remaining high-level functions, whereas a show of kindliness and fulfillment of their wants brought out

their best performance. In some there was great lability of affective expression, characterized by ready weeping and turbulent outbursts of rage. Even minimal effort was followed by pronounced fatigue. In the main, painful stimuli, threatening circumstances, catastrophic events, or even impending death were not significant to them and caused little reaction. On the other hand, sudden noxious stimulation frequently evoked an over-reaction of crying, rage, or violence. Passive dependence upon others was conspicuous.

In short, the behavior of those with severe diffuse atrophy may be considered as extreme manifestations of "Phase 4, or possibly merging into Phase 5" in impairment of the highest integrative functions. From the appraisal of patients not included in this series, a final phase (Phase 5) may also be defined. In this phase the patients were unable to walk, talk, or assume responsibility for normal self-care. They were incontinent of urine and feces and ultimately became stuporous and comatose.

Capacity to Withstand Repeated Failure

The procedures to assess the capacity to withstand repeated failure (described in Section I of "Results") were applied to 13 subjects with severe diffuse brain atrophy. They demonstrated a Stage 2 response after one to three failures. The Stage 2 response was characterized by quick, purposeless movements of arms and legs, such as wiping the brow, rubbing the eyes, or crossing and uncrossing the legs. Apparent also were sighing, licking the lips, and other facial grimacing.

Of these 13 subjects, 10 demonstrated striking perseveration of a wrong response, (Stage 3) beginning early and lasting throughout most of the procedure. Ten of these subjects became immobile except for lever pushing while perseverating a wrong response (Stage 3), and three persons went on to complete immobility, which lasted from 9 to 15 minutes. During this Stage 4 response, subjects sat quietly, motionless, staring at the wall or desk.

The average impairment score for these 13 subjects with diffuse brain damage was 340. One subject scored a maximum impairment score of 800.

In describing their feelings and reactions during Stages 3 and 4, these subjects stated that they were aware of despair and hopelessness and of wanting to "give up."

These subjects with diffuse and severe damage of the cerebral hemispheres became incapable of continuing goal-directed behavior early in a failure situation. They demonstrated perseveration of inappropriate behavior and became inactive, sometimes going on to immobility. Whereas intact subjects felt frustrated and resentful throughout the series of induced failures, these diffusely brain-damaged subjects relatively soon in the series described above had feelings of despair, hopelessness, and, finally, resignation during the phase of immobility.

In Table 17 have been listed and arranged those evidences of deterioration of the highest integrative functions in man as derived from the surveys of all the subjects including those with focal and diffuse brain damage made within the setting of home and work and from the more measurable performances in the laboratory. It does not indicate which functions are most fragile, nor does it show the magnitude of impairment, since it covers the range of dysfunction from least perceptible to major.

General Comment

The major conclusion from these studies is that the highest integrative functions are impaired after loss of tissue from the isocortex of the cerebral hemispheres, the degree of impairment being directly related to the mass of the defect regardless of site within the hemispheres.

Apparent exceptions to this general conclusion arise from the fact that the cerebral hemispheres include the projection areas as well as the isocortex. Hence, especially

TABLE 17.—*Evidence of Deterioration of the Highest Integrative Functions*

1. Impairment of Expression of Needs, Purposes, and Goal-Directed Activity
   - A. Reduced Expression of Affect
     1. Diminished expressions of feelings of satisfaction, joy, sparkle and spontaneity, love, support, friendship, and sympathetic understanding
     2. Behavior determined to a less extent by feelings of love, respect, and concern
     3. Report and description of less intense "feelings"; apathy
     4. Less show of warmth, with conspicuous but short lived abreactions, as seen in patterns of anger, hostility, resentment, and despair
     5. Reduced expressiveness, fluidity of communication, and response to humor and illusion
   - B. Reduced Interaction with the Environment — Avoidance of the New, Uncertain, Hazardous, and "Risky"
     1. Reduced seeking of challenge, adventure, stimulation, and novelty
     2. Reduced curiosity, inquiry, and pursuit of knowledge
     3. Establishment of rigid routines insuring ready success
     4. Reduced participation in diversions, entertainment, and in taking in news
     5. Reduced reaction to esthetic objects and activities
     6. Reduced participation and assumption of familial, vocational, interpersonal, and community responsibility
     7. Avoidance of excitement, the unfamiliar situations involving unexpected demands, poorly defined or unstructured situations, new situations, or situations involving the risk of failure, conflict, and fatigue
   - C. Impaired Pursuit of Values
     1. Diminished seeking of communication and recreation with others
     2. Reduction or abandonment of occupational and social goals — fall-off in "ambition"
     3. Lessened significance of abstract, impersonal, and altruistic goals
     4. Reduction of concern in the approval of others
     5. Reduction of disinterest and selfless, detached attitudes and behavior
   - D. Reduced Purposive Activity or Restless, Ineffective Overactivity
     1. Reduced intensity of activity — occupational, domestic, recreational
     2. Shortened periods of activity
     3. Less vigor, enthusiasm, and initiative
     4. Ready fatigability, with necessity for frequent rest periods
   - E. Reduced Expression of Simple Biological Needs
     1. Diminished eating of food, with inadequate diet
     2. Diminished pursuit of proper temperature, ventilation, shelter, and clothing
     3. Diminished pursuit of health, survival, and well-being of family and self
     4. Reduction in quantity and alteration in significance of sexual activity
2. Impairment of Mechanisms for Goal Achievement
   - A. Impaired Associative Capacity
     1. Reduced fantasy, creativity, imagination
     2. Poverty of alternate solutions after failure or frustration
     3. Reduced revery, and night dreaming, reduced imagery
   - B. Impairment of Alterness and Vigilance
     1. Difficulties in concentration and contemplation, focusing and sustaining attention, distractibility, difficulty, in perception with simultaneous irrelevant stimulation
     2. Diminished responsiveness, alertness, "consciousness," and awareness
   - C. Impaired Ability for Appropriate Inhibition
     1. Impulsive, unrestrained, unsuitable behavior
     2. Impatience
     3. Inability to brook postponement, frustration, and delay
     4. Impaired modulation of the expression of feelings, with
        - (*a*) irritability
        - (*b*) temper outbursts
        - (*c*) ready weeping
        - (*d*) assaultive, brash, and aggressive behavior
        - (*e*) excessive talk, laughter, etc.
        - (*f*) poorly maintained and rapidly dwindling attitudes, expressions and behavior
        - (*g*) altered response to noxious stimulation
   - D. Impaired Initiation
     1. Slow to get started, procrastination
   - E. Impaired Abstraction Capacity
     1. Defects in analysis and synthesis, poor comprehension of aphorism and metaphor, defective recognition of incongruity and non sequitur, defects in inductive and deductive logic
     2. Defects in planning, prediction, extrapolation, categorization
     3. Defects in ability to form concepts and see relationship; overliteral interpretations and impaired abstract thinking
     4. Defects in judgment
     5. Reduction in ability to extract recurrent and significant elements in changing situations
   - F. Impairment of Orientation
     1. Reduced exploratory and other orienting activity, reduced "incidental" perception
     2. Impaired orientation for time, place, person, and situation
   - G. Memory Defects
     1. Impaired recall of names and symbols promptly on demand, poor recording of current experience
     2. Defects in recent, intermediate, and remote memory and recall
     3. Difficulty in following conversations, or maintaining continuity in reading books, newspapers, etc.

TABLE 17.—*Evidence of Deterioration of the Highest Integrative Functions*—Continued

H. Reduced Learning Ability
   1. Slower rate of learning
   2. Reduction in complexity of learning achieved
   3. Lack of stability of learned responses
   4. Diminished ability to discriminate
I. Impaired Ability to Extinguish Responses
   1. Slower rate of extinction of responses when no longer appropriate
   2. Perseveration of responses
J. Impairment of Skilled Actions and Sensory-Motor Efficiency
   1. Slowing of action patterns
   2. Need for "conscious" control of action patterns that had previously been "automatic"
   3. Clumsiness, loss of skill, loss of "technical know-how"
K. Impaired Ability to Fulfill Social, Vocational, Interpersonal, and Community Responsibilities
   1. Impaired management of finances, allocation of responsibility, decision making
   2. Inability to take incisive action, or assign an order of importance to a series of acts
   3. Reduced ability for appropriate personal appearance, grooming, and social conventions
L. Impaired Perception of Self and the Self-Environment Relationship
   1. Impaired perception of social structure and interpersonal relationship
   2. Failure to perceive the import of actions and difficulties in their early stages
   4. Impaired awareness of success and failure
   5. Impairment of perception of the import of actions to others and the possible consequences and ramifications of one's actions
M. Impaired Perception of the Environment
   1. Vague, slow, and distorted perceptions
   2. Difficulties in discrimination between the effects of sensory stimulation and of sensory "fantasy"
   3. Need for greater stimulus intensity for perception
   4. Increased suggestibility
   5. Ready "confabulation"
   6. Need for strong contrasts between stimuli for differences to be perceived

3. Impairment of the Capacity to Initiate, Organize, and Maintain Appropriate and Effective Adaptive Reactions
   A. Evidence of failure or inadequacy of defenses (*a*) anxiety, depression; (*b*) bizarre, illogical, and highly personalized perceptions; (*c*) conspicuous, transparent, splintered, and socially unacceptable defensive reactions; (*d*) poorly elaborated and inappropriate compensatory reactions.
   B. Evidence of excessive display of defenses (excessive blaming, projection, suspiciousness, social withdrawal, and constriction of activities and interests, compulsive activity, perfectionistic striving; denial; depersonalization; reaction formation, etc.

4. The Capacity to Maintain Organization During Stress and to Recover Promptly from Its Effects
   A. More ready disorganization during periods perceived as threatening, as in situations of failure, postponement, assault or betrayal, changes in intimate interpersonal relationships, conflict, fatigue, isolation, etc. with evidence of "blocking," "catastrophic" reactions and feelings of anxiety; severer disorganization following deprivation of food, sleep, warmth, sexual satisfaction, human companionship, support, and approval
   B. Longer-lasting and severer disorganization following the above, with necessity for longer periods of recovery
   C. Reduced tolerance for alcohol, oxygen lack, and noxious chemical agents
   D. Enhanced susceptibility to perceptual distortions, hallucinations, illusions, delusions and delirium; increased seeking of support, encouragement, praise, and approval

with resection of nonfrontal regions of the hemispheres, lower level functions are almost inevitably impaired, and therefore subjects with large nonfrontal lesions have higher total impairment scores than do subjects with similar mass defects in the frontal region. Damage to the postcentral area is followed by hypesthesia and defects in the synthesis, interpretation, differentiation, and comparison of the effects of sensory stimulation. Lesions of the calcarine cortex of the occipital lobes or of the optic radiations leading to the calcarine cortex result in visual field defects. Relatively small lesions in the left hemisphere of right-handed subjects may be followed by defects in speech, writing, reading, and calculation. Teuber [181] made studies on patients who had sustained physical traumata of the brain. The major defects were in one hemisphere, although possibly pathological changes were not limited to the side of major injury. Sensation was impaired in the hand opposite to the side of major brain injury, but no impairment in simple sensory function in the hand corresponding to the ostensibly intact hemisphere was demonstrable. The blindfolded subject was allowed to palpate a particular three-dimensional form and then permitted to palpate in sequence six different forms by having each pressed into his palm for 5 seconds. He was asked to identify the one he had first felt. Impairment of object

discrimination was most evident in the hand with gross sensory loss, but impairment was also significant in the other hand. Similar results were obtained in tests involving visual discrimination. In other words, a lesion anywhere in a hemisphere interfered with this kind of learning. The generalized visual impairment of subjects with hemianopsia contributes to difficulty in calculation.

Patients with partial or complete hemianopsia showed that the visual functions in the remaining intact field were impaired in some degree. For example, a seamstress whose right occipital lobe had been removed complained that she no longer could make rapid discrimination of black thread against black cloth and that she had difficulty in visualizing a completed dress from a pattern or sketch. In other regards, the degree of impairment, as indicated by appraisal of adaptive capacity outside the laboratory, was similar for those with large nonfrontal lesions and those with equally large frontal lesions. On the other hand, in the laboratory, while no differences were found, mass for mass, on most procedures between the performance of subjects with small frontal lobe lesions and those with small nonfrontal lobe lesions, those with large nonfrontal lesions performed less well mass for mass than did those with large frontal defects. Moreover, analysis of the responses to the Rorschach ink blots indicated that subjects with even small nonfrontal lesions performed less well on tasks requiring visual imagery and fantasy than did those with frontal lobe lesions of comparable extent. Since almost all of the laboratory procedures involve visual functions, it is inferred that this greater impairment mass for mass observed in laboratory testing of subjects with nonfrontal lesions stems from the limitation of visual functions found in these subjects. This inference is supported by the fact that the subjects with large nonfrontal lesions who performed most inadequately had major visual field defects (Table 10).

The New York Hospital data suggest that the projection areas, as well as the isocortex, contribute to the complex of highest integrative functions. But since the criteria of assessment of performance become invalid in the face of major fall-off in sensation, motility, and speech functions, no definite inference may be drawn about the contribution of these areas.

The generalization that the highest-level functions in the patients of this study were impaired after loss of tissue from the isocortex regardless of site and in proportion to the mass of defect is contrary to the inferences of Halstead[124,125] and of Rylander,[122,123] who concluded that the damage to the frontal lobes led to greater impairment of highest-level functions than did nonfrontal lesions of similar mass. It is our opinion that this conflict is one of interpretation rather than of observation. The discrepancy can be resolved by reconsideration of the mass of tissue removed in the subjects in the studies of these investigators. Halstead's method of appraisal of the extent of lesion was based on the area of the excised cortex as outlined on graphic representations of the brain in several planes. According to our view, his method leads to an overestimation of the mass of the temporal lobes and an underestimation of that of the frontal lobes. With Halstead's method of appraisal, a patient with a frontal lobectomy extending posteriorly to the precentral gyrus (for example, Halstead's Cases 52-54, 57, 61-68) is assigned an average "% lesion score" of 14.3, whereas a patient with a total temporal lobectomy (for example, Halstead's Cases 9 and 43) is assigned an average of 15.9, thus indicating that these lesions are approximately the same size. However, Addison and Donaldson[152] find that the frontal lobe cortex accounts for 37.9% of the volume of the cortex, whereas the temporal lobe cortex is approximately one-half as large (15.1%). This proportion of 2:1 between the mass of the frontal lobe cortex and the mass of the temporal lobe cortex is in good agreement with the measurements of the weight of ex-

cised portions of the cerebral hemisphere made in the laboratory of the New York Hospital. Halstead's overestimation of the temporal lobe lesions in proportion to frontal lobe lesions is particularly significant, since the majority of the lesions in Halstead's nonfrontal subjects (25 of 37) are located in the temporal lobe. As a matter of fact, many of these nonfrontal subjects had had resection of the anterior 5-7 cm. of temporal lobe—as therapy for psychomotor seizures—a procedure that removes only from 30 to 60 gm. of hemispheric tissue. When on the basis of Halstead's published drawings the mass of tissue loss of his subjects was reestimated, according to the data of Addison and Donaldson and of the New York Hospital, and expressed in grams, it was evident (Fig. 6) that the degree of impairment mass for mass observed in Halstead's subjects with nonfrontal lesions was approximately equal to that observed in his subjects with frontal lesions. Further, Halstead's series includes only one subject (Case 91) with loss of nonfrontal hemispheric tissue equivalent in mass to that removed in a frontal lobectomy extending as far back as the precentral gyrus.

Shure and Halstead [125] inferred that only tests having to do with the capacity to elaborate abstractions were performed significantly less well by subjects with frontal lesions than by those with nonfrontal lesions. This inference is a modification of an earlier conclusion that subjects with defects in the frontal lobe exhibited greater impairment than did those with lesions elsewhere on a wide variety of test procedures. The principal tests (1, Table 2) used for assaying of "abstraction" and 5, are the most sensitive and readily impaired of all the procedures employed. It is to be expected, therefore, that these sensitive procedures would best reflect the difference in performance between large and small lesions regardless of site. This observation by Halstead that the difference between frontal and nonfrontal groups was most apparent for tests of "abstraction" therefore does not necessarily indicate that "abstraction" is related specifically to the frontal lobes. It may merely reflect that a larger proportion of the mass of the cerebral hemisphere is contained within the frontal lobes than within any other single lobe. In other words, from reevaluation of Halstead's data, we find support for the view that destruction of equivalent mass of hemispheric tissue in the nonfrontal regions results in similar impairment of abstraction capacity. As a matter of fact, in the New York Hospital series, destruction of a large mass of tissue in nonfrontal regions resulted in an even greater impairment mass for mass than was noted in subjects with frontal lobe defects. Conceivably, this resulted from impairment of visual function, as mentioned previously.

Rylander's inference [126] that greater impairment of highest integrative functions occurs in subjects with frontal lobe lesions as compared with subjects with nonfrontal lesions may be explained similarly. He found on assay procedures related to solving of abstract problems that if one waives consideration of mass, performance of subjects with frontal lobe lesions was impaired. In contrast, the performance of those with nonfrontal injuries was not impaired. However, when Rylander's data are arranged so that mass is considered, several relevant relationships become evident. First, no subjects with nonfrontal lesions comparable in size to the larger frontal lesions are included. Second, neither the subjects with small lesions in the frontal lobe nor those with the same-sized lesion in the nonfrontal regions showed impairment. Third, of the subjects with frontal lobe defects, only those with large mass defects were significantly impaired, and therefore could not be contrasted with subjects with large nonfrontal lesions. Apparently Rylander's assay procedures were too insensitive to detect impairment in subjects with small lesions.

The data of the New York Hospital study do not support the view that there is a "frontal lobe syndrome" consisting of major impairment of specific features of the highest integrative functions. Yet major im-

pairment of highest integrative functions in the absence of significant motility or sensory defects in a patient with focal disease does point to a frontal lobe defect. To resolve this seeming conflict, it may be pointed out that "the frontal lobe syndrome," as usually defined, refers to a group of defects that occur only after a relatively large mass of tissue is damaged: Defects of mass in nonfrontal regions sufficiently large to produce grossly apparent impairment of the highest integrative functions inevitably result in significant defects in motility and sensation as well, thus indicating the location of the lesion. Usually with such evidence the clinician would make no further investigation of details of the subject's behavior that might reveal moderate impairment of the highest integrative functions. In the study at the New York Hospital such impairment of highest integrative functions in those with nonfrontal lesions has been discerned, when sought. But in a given subject with a small nonfrontal lesion, significant disturbances in sensation and motility may be present with only minimal impairment of highest-level functions.

Many studies on laboratory animals have been interpreted as indicating that the activity of specific neuronal aggregates in the cerebral hemispheres determines unique qualitative features of high-level functions. The best defined of these relationships has been that the capacity of monkeys to perform "delayed-response" problems is greatly impaired after bilateral frontal damage. This observation has been interpreted to mean that memory functions are specifically related to the frontal lobe cortex, since bilateral removals of comparable mass elsewhere in the cerebral hemisphere do not result in defects as striking as those following frontal lobe lesions.[103] However, it was subsequently found [153] that a number of alterations in method (turning off the light during the delay period, sedation with pharmacologic agents, or seemingly minor modification in details of the procedure) that would not be expected to aid memory functions improved the capacity to perform the test, and in some instances eliminated the difference in performance between monkeys with frontal and those with nonfrontal lesions. The defective performance of the monkeys with frontal lobe lesions may therefore be a consequence of the greatly increased spontaneous activity and circling movements characteristic of monkeys with frontal lobe lesions. Spontaneous activity of monkeys after bilateral frontal lobectomy may be increased as much as 17 times (Symmes [179]).

This hyperactivity may also obscure the measurement of the impairment of other functions. For example, it has been pointed out that monkeys after removal of temporal lobes bilaterally engage in less exploratory activity. Monkeys after removal of frontal lobes bilaterally do not show this lack of exploratory activity. This fact has been cited as evidence of impairment of specific high-level function in animals with temporal lobe defects.[154] But the restlessness and over-activity of monkeys after frontal lobectomy may interfere with the assay of exploratory activity, and therefore the differences in behavior between the two groups of experimental animals may be apparent rather than real, and an aspect of methodological difficulty.

The Klüver-Bucy syndrome observed after bilateral lesions of the temporal lobe includes major alterations in behavior that are not observed after lesions elsewhere in the cerebral hemispheres.[155] However, Klüver and Bucy's resections induced extensive damage in the archipallium, as well as in the temporal lobe cortex. Bilateral removal of only the temporal lobe cortex does not produce the characteristic features of the syndrome. On the other hand, the syndrome can be induced in whole or in part by selective damage to archipallial structures in the absence of damage to the overlying cortex of the temporal lobe. Therefore, the evidence presented by Klüver

and Bucy is not out of keeping with the facts of the New York Hospital study.

It is of interest that even in procedures for assessing relatively simple sensory functions impairment has been found in laboratory animals to stem from defects in regions outside the projection areas. Thus, impairment of auditory and visual discrimination has been noted in monkeys with frontal lobe defects, and those with temporal lobe defects have been found to have impaired visual discriminations.[153] Although in monkeys the defects in visual discrimination with lesions of the calcarine cortex of the occipital lobe can be demonstrated predictably, no comparable auditory impairment has been demonstrated following even extensive bilateral lesions involving the auditory projection cortex. In brief, ablation experiments on laboratory animals have not demonstrated that qualitatively different features of high-level function are related to specific sites within the cortex. Further, they indicate that large lesions of the isocortex remote from projection areas may impair performance on perceptual tasks, much as they do in man.

The results of these studies at the New York Hospital do not justify the inference that those who are endowed with heavier brains are necessarily those with the greatest potential as regards the highest integrative functions. Indeed, the weight of the brain of normal intact human subjects varies within wide limits (approximately 900 to 1,800 gm. total brain weight [156]), and there is no discernible relationship between the intact brain mass and the quality of highest-level functions.[157] This suggests that in a given subject it is the number of cells lost and the subsequent interruption of patterns of connection that is critical in determining the degree of impairment.

The inferences drawn in the preceding concerning the nonspecificity of particular areas of the isocortex for the highest integrative functions are in keeping with the homogeneous histological appearance of the isocortex and with what is known of the extensive degree of cellular interconnections within the cortex.[65] About 7,000,000,000 nerve cells are arranged in orderly layers in the cerebral cortex, and 70% of their tangential fibers traverse the hemispheres and interconnect in one way or another.[158] The average nerve cell has about 5,000 direct contacts, the larger cells having even more. A single nerve cell in the cerebral cortex may receive on its surface as many as a hundred terminals from various other cells, and probably the majority of the cortical nerve cells connect directly or indirectly with every cortical field. Herrick [159] attempted to get some conception of the number of possible connections among these billions of cortical cells. On the basis of a series of computations he inferred that there were $10^{2,783,000}$ such connections, an incomprehensibly large number. The cytopathological implications of this degree of interconnection are suggested by the experience of Yakolev,[160] who noted widespread changes in the cerebral cortex following the removal of even highly circumscribed portions of the frontal lobes. Similarly, Torres [161] noted a reduction of alpha rhythm in the electroencephalogram following removal of portions of the cerebral hemispheres. The degree of this reduction was roughly proportional to the extent of the tissue loss, regardless of the site from which the tissue had been removed.

However, other contemporary studies have led to the inference that the activity of local neuronal aggregates results in specific features of the highest integrative functions. Penfield [163-166] has shown that in some patients with epileptic seizures, memories can be evoked by electrical stimulation of parts of the cortex of the temporal lobe and *only* that portion of the cerebral hemispheres. This observation is not out of keeping with the inferences derived from the New York Hospital series if it is appreciated that local excitation of the temporal lobe of the cerebral hemispheres by electrical means sets up disturbances in patients with epilepsy, which then spread widely in their effects to other parts of the hemispheres. Such ready spread

may account for the observations that some patients with temporal lobe lesions and psychomotor seizures have serious impairment of highest-level functions.[162] The memories evoked and the disturbance of consciousness that also follows, then, may be both manifestations of a diffuse disorder in function of the cerebral hemispheres in epileptic patients. This interpretation of these experiments using stimulation is supported by the observations in the New York Hospital series that impairments of memory result from damage in any region of the cerebral hemispheres, the degree of the impairment being closely related to the mass of brain that is damaged.

Penfield's stimulation experiments focused attention on the temporal lobes, and it was at first implied that the "store of memory" was in the cortex of the temporal lobe. Since the removal of the neural tissue that, when stimulated, evoked recollections of past experience did not result in loss of memory for the episode recalled during stimulation, it was suggested that the two temporal lobes stored simultaneously. Later it was found that even bilateral anterior temporal lobectomy failed to result in profound memory loss. It was then suggested by Penfield and Milner,[167] Scoville and Milner,[168] and Sweet and associates[169] that the rhinencephalic structures, hippocampus, amygdala, and fornix, are especially concerned with memory, and subjects who developed severe memory defects following bilateral destruction of these structures have been reported. Such studies have not fully taken into account the total range of neural structures implicated in the patients reported. Indeed, Bengochea et al.[170] showed that small lesions restricted to the fornix do not result in striking impairment of memory. The total extent of the brain is important, since memory defects comparable to those reported as occurring after removal of the third-ventricle cysts or after bilateral hippocampal resections occur in subjects with major loss of tissue from the cerebral hemispheres regardless of site.

In our opinion, formulations that ascribe a limited aspect of the highest integrative functions, such as memory, to the activity of specific neuronal aggregates have stemmed from (1) neglect of other aspects of impairment because of a too narrow conception of highest integrative functions and inadequate methods of assessment, and (2) lack of consideration of the total extent of the lesion in these patients. For example, it has been suggested by some that the striking impairment of recent memory of patients with Korsakoff's syndrome found in patients with chronic alcoholism results mainly from the lesions about the third ventricle, so conspicuous in Wernicke's disease. However, limiting the impairment to memory is erroneous, since patients with this syndrome are strikingly impaired in many ways, in addition to memory loss, if one takes into account their performance in the extralaboratory setting. Their family, friends, and employers find them incapable of assuming their responsibilities and in meeting the usual demands of their interpersonal relationships. In laboratory testing procedures the fall-off in recent memory is striking, but also impaired are the capacities to establish stable conditioned reactions, to maintain stable discriminations, and to learn. Similar considerations apply to the several studies that describe the "amnestic syndrome" in patients with lesions in the archipallium. The loss of recent memory is an easily recognizable defect evident after even a few moments' exchange with the patient; its dominance may overshadow other features of impairment. Also, psychometric tests do not assess many of the features of deterioration in the highest integrative functions, and therefore they, too, give an incomplete picture of the range of impairment. However, when the highest integrative functions are assessed also by extensive investigation of the behavior of the patient in his usual setting, it is evident that the over-all impairment is by no means limited to memory in subjects with the

"amnestic syndrome." "Memory" is but one of the functional constellations disrupted.

Secondly, the disturbances in neuronal function and structure in the brain of patients with the Korsakoff's syndrome are not limited to the periventricular region and midbrain but involve much of the brain. Also, since patients operated upon for neoplastic disease in the region of the third ventricle sustain injuries of other parts of the brain in the process of approaching the tumor, the total mass of cerebral tissue implicated in these patients is usually ill defined, but extensive.

In brief, important midbrain communications and activation systems essential to proper function of the hemispheres are damaged by lesions in the head end of the brain stem and secondarily lead to impairment of the highest integrative functions by depriving the neurons of the cerebral hemispheres of proper support. But that this region contains the particular neuronal aggregate for memory, or, more specifically, "recent memory," does not follow from the evidence adduced to date.

Whenever a subject in the New York Hospital series who had sustained loss of brain tissue exhibited bland affect, remarkable freedom from anxiety, indifference about his responsibilities and of the consequences of his acts, or apathy, such a subject was also unlikely to complain of sustained pain from any cause. This impairment of reaction to sustained noxious stimulation was not accompanied by loss of pain perception, and indeed the subject was capable of, and likely to have, a quick and often violent reaction to a suddenly induced, short-lived, or even low-intensity noxious stimulation.

Recent studies [171] have been interpreted as indicating that the mass of defect is not directly related to the reduced reaction to pain. These conclusions were based on patients who exhibited indifference to sustained noxious stimulation after having portions of the frontal lobe damaged by coagulation procedures. However, the inference is difficult to assess, since it was not possible to give precise information as to mass of defect or the state of the patient after the lesion was made. The failure to note a relationship between the extent of the lesion and the alteration in reaction to noxious stimulation may have stemmed from a smaller range of variation in lesion size in this [171] study than in that of the New York Hospital series. In the latter series (in which the mass of tissue loss varied from 15 to 150 grams) the relation between the mass of tissue loss and the magnitude of impairment in reaction to noxious stimulation was a direct one when the loss of hemispheric tissue regardless of site, was greater than 90 grams. The phenomenon of impaired reaction to noxious stimulation was linked in all instances with paucity or other disturbance of the expression of affect. It was not dependent upon sectioning of specific frontothalamic pathways.†

Application of current to electrodes placed in certain defined areas of the brain [172] has been reported to result in striking changes in behavior, with reports of pleasurable feeling when the electrodes were placed in some sites and unpleasant feelings when placed in others. Since such stimulation results in disturbances of unknown extent within the brain, it is difficult to appraise their significance as regards participation of specific cell aggregates in particular features of the constellation of the highest integrative functions.

Formulation

The Nature of the Highest Integrative Functions.—Integration, stemming from the Latin, "integrare," "to make whole," has been used here not only to mean the putting together of parts to make a whole but also

† Two patients studied at the New York Hospital with lesions in the right occipital-parietal region especially and dramatically demonstrated such altered reaction to noxious stimulation. The first of these had lost 90-120 gm. of cerebral tissue. The second patient had lost over 200 gm. of cerebral tissue. Other data from this patient have not been included in the analysis of the performance of those with focal lesions.

to imply that the linking of separate functions of the nervous system results in new kinds of functions and not mere combinations of simple elements. Also, it is assumed that intermediate and lower levels of function, activated, inhibited and modulated by higher ones, make their contribution to the synthesis of entirely new functions. In other words, the patterns integrated at spinal and brain-stem levels are dominated by the myriad patterns synthesized at the cortical level, but these are, in turn, integrated not only with each other but also with the effects of stimuli from within and without the central nervous system with the effects of past experience. This integration in its most elaborate form makes possible those features characteristic of man alone.

Survival for man depends upon his ability to meet myriad new situations. He must have the capacity to endure periods of transition and to persist, return to the task, and recover promptly from the effects of failure, frustration, postponements, and difficult discriminations. These capacities call for a special set of highest integrative functions that supplement learning, recognizing, knowing, remembering, relating, and planning. These functions have to do with the maintenance and restoration of organization and serve to restore proper speed of response quickly, lend continuity, and maintain stability during periods of stress. They are subtle, sensitive, and readily impaired. Evidences of their decline are among the first to be noted in deteriorating behavior of humans.

Unfortunately, no word in common usage is suitably inclusive to embrace the broader aspects of deterioration of the highest integrative functions. "Dementia" is inadequate for several reasons, most importantly because the word has a mental connotation, i. e., orientation, memory, judgment, and learning. While such mental functions as these often are impaired following damage to the cerebral hemispheres, this is not striking unless the damage is relatively severe (in this series more than 120 gm. of tissue loss). However the same subjects and even those with as little as 30 gm. of tissue predictably demonstrated defects in other aspects of their adaptive capacity. Hence, equally important are other defects in the highest functions, also described above, such as lowered thresholds and diminished tolerance for frustration and failure, impaired capacity to maintain performance during stress and to recover quickly from the effects of stress, as well as impaired capacity to maintain effective and appropriately modulated patterns of defensive behavior.

Four categories of highest level functions have been recognized (Table 17). First are those functions having to do with the expression of needs, appetites, and drives. Fall-off in these functions is manifest in decreased seeking of challenge and adventure, restriction of imagination, lessened human association and exchange, diminished aspiration and striving, abandonment of previously cherished goals, passive acceptance of circumstances, lessened sexual activity, and, when the damage is severe, inadequate response to even the minimal requirements of food, shelter, and warmth.

Second are those functions having to do with the capacity to respond to symbols as substitutes for biologically significant events —thus employing effectively the mechanisms for goal achievement. These enable the individual to anticipate dangerous or propitious circumstances and to learn, remember, perceive, know, arrange, plan, invent, explore, postpone, modulate, and discriminate. Also in this category is the capacity to eliminate responses when they are no longer appropriate.

Third are those functions that enable man, under circumstances of duress, to integrate elaborate behavior patterns of a defensive or protective nature that are appropriate, adequate, socially acceptable, and sustained.

Fourth are those functions having to do with the maintenance of organization. These, as mentioned above, serve to lend continuity and maintain stability and proper

speed of response, especially important during periods of stress.

Though the brain does, of course, function in general as a unit, each part dependent upon the adequate functioning of the remainder the neocortex, the most recently developed portion of the cerebral hemispheres, serves as the central integrator for over-all adaptation—and adaptation for man must include creating, the ability to withstand changes and threats, the pursuit of adventure, exploration of the new, and, above all, aspiration.

Phases of Consciousness, the Highest Integrative Functions and the Brain Stem.—Top performance in highest level function is dependent on the proper interaction of an individual with his environment. Cutting off even for hours or days most incoming stimuli,[173] i. e., from the eyes, the ears, the nose, the skin, and joints and muscles, may seriously alter the capacity to function at the highest level, and such impairment may persist for a variable period after return to the usual environment.

To what extent can the newer portions of man's cerebral hemispheres be damaged or removed, and man still be partially conscious and exercising to some degree his highest integrative functions? Consciousness is not an all-or-none phenomenon, but one with myriad levels. Thus, the barest response to painful stimuli or loud shouts gives evidence of some consciousness, whereas impairment may be revealed in minor and ill-defined disturbances in perception and lapses in attention. Laboratory animals exhibit some degree of responsiveness in the absence of one or even most of both cerebral hemispheres. In man, too, considerable portions of one or both hemispheres can be removed without complete loss of consciousness; and when one hemisphere is badly damaged in infancy, it can be removed in later life without additional impairment. But massive destruction of both cerebral hemispheres, as by asphyxia, is followed by a permanent loss of all but the most primitive responses. Broadly speaking, there is a direct relationship between the amount of tissue damage within the cerebral hemispheres and levels of consciousness.

Extensive damage bilaterally in the archipallium [174] results not in stupor, coma, or lethargy but, rather, in a seriously altered consciousness, with the exhibition of complicated but poorly integrated and socially unacceptable patterns of behavior.

Pressure upon or puncture of the caudal part of the brain stem results in prompt loss of consciousness. Damage of the midbrain can result in serious disturbances in consciousness, verging on stupor or coma. The subject may look alert and responsive because his eyes are wide open, but he makes few movements and no utterances.[175] Also, injury to the immediate neighborhood of the midbrain and to structures slightly farther forward may result in excessive sleepiness.[176] These observations have led recently to revival of the concept of the brain stem as the "center of consciousness." [177] A more attractive assumption is that stimulation of the brain stem-activating system, by enhancing responsivity of neurons in the cerebral hemispheres to the effects of incoming impulses from the sensory end-organs, facilitates activity in the cerebral hemispheres, whereas injury to the brain stem deprives the cerebral hemispheres of these enhancing effects.*

* Interesting instances of the enhancing effects of brain stem stimulation are to be found in the many experiments reviewed in a recent symposium and especially by the self-stimulating phenomena exhibited by rats with electrodes or pipettes placed in these regions. Self-stimulation maneuvers repeated at varying intervals by some animals so prepared may persist indefinitely.[182]

Also, experiments with electrodes within the brain substance indicate that much of the brain in a conditioned laboratory animal is activated by the conditioning stimulus. Thus, during exposure to conditioning auditory stimuli, there have been demonstrated electrical disturbances at the earliest synaptic level in the brain—the cochlear nucleus, in the reticular formation, in the limbic system and at the cortical level.[183] However, this widespread involvement does not detract from the significance of the isocortex in the organization of the highest integrative functions.

In short, damage to the human brain stem and neighboring structures alters "consciousness" and impairs the highest integrative functions by depriving the cerebral hemispheres of necessary support. But, assuming proper support from other parts of the body and the lower levels of the nervous system, the full expression of the highest level of activity of the nervous system, achieving for man maximum adaptive versatility, is dependent ultimately on the proper functioning of the intact cerebral hemispheres.

The Steps from Nerve Cells to Adaptive Behavior in Man.—Can one link what is known of the functions of a neuron with what is evident about highest-level brain functions? In its structure and function a neuron offers us no clues, except in its conspicuous irritability and its many connections.

On the irritability of neurons reflexes can be built, and in simple systems there is a direct relationship between input and output. Complex reflexes are built by combining simpler ones.

But the concept of the reflex is less applicable to the highest integrative functions, where there is no direct relationship between input and output. Responses are long delayed and are dependent upon countless previous experiences, and variations in the circumstances during stimulation make the output unpredictable.

The demonstrable relationship between the highest integrative functions and the whole mass of ordered aggregates of neurons in the cerebral hemispheres does give a clue to the nature of highest-level integration. Whereas removal of small amounts of the hemispheres from any region does not abolish the highest-level functions, it does reduce the capacity for the most complex human activity. It follows as a reasonable assumption that the number and arrangement of nerve cells are of central importance.

In other words, when tremendous numbers of neurons are arranged compactly, and in an extremely complex relation to each other in the cerebral cortex, they acquire through interaction properties quite different from those of single neurons or neurons in smaller groups. In this ordered relationship of an enormous number of cells, phenomena arise which are as different from the functions of the individual neurons as are the properties of protoplasm from its basic constituents. Thus, the aspect of brain tissue pertinent to the highest-level functions is not so much location within the hemispheric mass, or connections with peripheral structures, as it is the absolute number of ordered arrangements within the tissue mass. The fact that each neuron may influence many other neurons, some of which are remote, suggests that the "order" of brain tissue is not simply the "checkerboard" order of classical thermodynamics, which lacks an extensive dimension but, rather, is like the "order" of an aperiodic crystal. The huge number of stable interconnecting neural arrangements possible within the brain indicates that the "arrangement density" of the human brain is vastly greater than any analogous physical apparatus suggested to date.

The property of being highly ordered, is of course, not limited to the brain, but is shared by all living cells. The density of arrangement within different bodily tissues varies greatly, reaching its apex in the brain. Although all tissues contribute, it is suggested that, by virtue of this high density of arrangement and their great mass, the cerebral hemispheres of man contribute more to mind than do other bodily structures. In a sense, then, "mind" resides in every cell of the body, a view in keeping with the intuition of the ancients, who were reluctant to name the brain or any single organ as the sole residence of mind.

Basic needs originate in many parts of the body, and the highly organized brain serves to fulfill them. But, being itself an organ within the whole creature, the brain also has a need of its own, the requirement that the organism operate in a setting that permits of proper interaction with the environment. Without this the brain fails.

The concept that the organization of highly ordered systems is featured by purposive, self-regulatory, goal-oriented activities is in keeping with the contemporary orientation of biologists. Thus, Sinnott [178] defines mind as "whatever directs the development of an organism towards goals set up within its living stuff."

Accordingly, the relationship of the brain to the mind may be epitomized as follows: Mind is the aggregate of purpose and needs, arising from the parts and the whole of the human organism, whereas the brain in addition to contributing to purpose, is the organ of means for maximum adaptive versatility to achieve these ends.

Summary and Conclusions

1. The site of tissue loss within defined areas of the cerebral hemispheres was of major significance as regards impairment or lower-level functions (simple motility and sensory functions). Indeed, serious impairment of these functions resulted even when small amounts of cerebral tissue were destroyed in these specific regions, and there was less impairment when loss of comparable extent occurred in other regions of the cerebral hemispheres. Moreover, the site and side of tissue loss were relevant to such intermediate functions as speech, reading, writing, and relatively simple visual-motor functions.

2. Through studies of persons with loss of known amounts of tissue from the cerebral hemispheres, four categories of the highest integrative functions were defined as follows: (*a*) the capacity to express needs, appetites, and drives; (*b*) the mechanisms for goal achievement (learning, memory, categorization, modulation etc.); (*c*) the capacity to initiate, organize, and maintain appropriate adaptive reactions; (*d*) the capacity to maintain organization during stress and to recover promptly from its effects.

3. Subjects with loss of given amounts of tissue showed significant variations in the degree of impairment of the highest integrative functions. Impairment was less in those who premorbidly had demonstrated a high order of adaptive versatility and greater in those who before the loss of brain tissue exhibited prolonged difficulties in over-all adaptation with much anxiety. The individual variations in degree of impairment were more striking when the mass of cerebral tissue loss was small (less than 60 gm.) and less evident when the mass of cerebral tissue loss was great (90 to 150 gm. or more focally.

4. However, in a series in which the premorbid over-all adaptive capacities were comparable and the mass of tissue loss varied from 15 to 150 gm., the form, the content, and the degree of impairment of the highest integrative functions were directly related to the mass of cerebral tissue lost from the isocortex and were independent of site and side. All apparent exception to this general principle was shown by subjects with large nonfrontal lesions who were somewhat more impaired than were those with similarly large frontal lesions. It is inferred that impairment of lower and intermediate level functions in subjects with large nonfrontal lesions is responsible for this difference.

5. Also, studies of patients with various but less well defined degrees of diffuse loss (from slight to severe) of tissue from the cerebral hemispheres demonstrated a direct relationship between the amount of tissue loss and impairment of highest integrative functions. Individual variations were less striking in those with moderate to severe diffuse tissue loss.

6. An implication of this principle of mass action of the cerebral hemispheres is that the degree of impairment of the highest integrative functions is directly related to the total number of inadequately functioning cortical neurons regardless not only of site but also of whether the defective neurons are aggregated in one area of the isocortex or diffusely distributed throughout the hemispheres.

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Appendix

A more complete presentation of the data of this study is included in an Appendix, which does not appear in the published article but will be included in reprints of it. The following is a list of the tables that appear in the Appendix.

Table 18: Raw Scores of 25 Intact Subjects for the Components of the Halstead Aggregate

Table 19: The Intercorrelations Among the 10 Components of the Halstead Aggregate and the Correlation of Each Component with Age and with (Henman-Nelson) I. Q., Based on the Scores of 25 Intact Subjects

Table 20: Raw Scores of the New York Hospital Series for the Halstead Aggregate (Nonfrontal, 24 Subjects)

Table 21: Raw scores of the New York Hospital Series for the Halstead Aggregate (Frontal, 21 Subjects)

Table 22: Standard Scores of the New York Hospital Series for the Halstead Aggregate (Nonfrontal, 24 Subjects)

Table 23: Standard Scores of the New York Hospital Series for the Halstead Aggregate (Frontal, 21 Subjects)

Table 24: Standard Scores of the University of Chicago Series for the Halstead Aggregate (Nonfrontal, 25 Subjects)

Table 25: Standard Scores of the University of Chicago Series for the Halstead Aggregate (Frontal, 19 Subjects)

Table 26: Means, Standard Deviations and Correlations with Mass of Tissue Loss for the Data of the University of Chicago Series for the Components of the Halstead Aggregate (Small Frontal, Large Frontal, Small Nonfrontal, 44 Subjects)

Table 27: Means, Standard Deviations and Component Intercorrelations and Correlation with Mass of Tissue Loss for a Pooled Series of 88 Subjects for the 10 Components of the Halstead Aggregate

Table 28: Intercorrelations of the 10 Components of the Halstead Aggregate for the New York Hospital Series (45 Subjects) and for the University of Chicago Series (44 Subjects)

Table 29: Factor Analysis of the 10 Components of the Halstead Aggregate Based on the Scores of 48 Subjects with Loss of Tissue from the Parietal, Temporal, or Occipital Lobes

Table 30: Factor Analysis of the 10 Components of the Halstead Aggregate Based on the Scores of 40 Subjects with Loss of Tissue from the Frontal Lobe

Table 31: Factor Analysis of the 10 Components of the Halstead Aggregate Based on the Scores of 88 Subjects with Loss of Tissue from the Cerebral Hemispheres

Table 32: Raw Scores of the New York Hospital Series for the Wechsler-Bellevue Aggregate (Nonfrontal, 24 Subjects)

Table 33: Raw Scores of the New York Hospital Series for the Wechsler-Bellevue Aggregate (Frontal, 21 Subjects)

Table 34: Intercorrelations of Subtest Scores on the Wechsler-Bellevue Aggregate, (45 Subjects with Loss of Tissue from the Cerebral Hemispheres)

Table 35: Raw Scores of Ratings of Responses to the Rorschach Ink Blots (Nonfrontal, 17 Subjects)

Table 36: Raw Scores of Ratings of Responses to the Rorschach Ink Blots (Frontal, 14 Subjects)

Table 37: Intercorrelations of the 28 Criteria for Rating the Responses to the Rorschach Ink Blots Based on the Responses of 31 Subjects with Loss of Tissue from the Cerebral Hemispheres

Table 38: Raw Scores on the Conditioned Reaction Procedure (Nonfrontal, 18 Subjects)

Table 39: Raw Scores on the Conditioned Reaction Procedure (Frontal, 23 Subjects)

Incidence of Anomalies of the Circle of Willis in Psychiatric Patients

DONALD L. HOWIE, M.D., Newtown, Conn.

The role of variations in the circle of Willis in brain diseases is unknown. They can alter angiograms and the results of carotid surgery. But do they contribute to diseases of the brain and to psychiatric disability?

A major problem in evaluating this question is variation in quoted percentages of anomalies. These variations arise in part from differences of opinion as to what constitutes a real change in anatomy. An observer tends to record those changes which he thinks will alter the circulatory pattern.

The following study was undertaken to find relationships that might exist between anomalies of the circle of Willis and other clinical or pathological data.

Material

Anomalies were recorded in 139 randomly selected general hospital autopsies done at Kern General Hospital, Bakersfield, Calif., and in 256 almost consecutive psychiatric hospital autopsies done at Fairfield State Hospital. All cases were examined by one person (myself) during a period of constant interest in the structure. In neither series were minute thread-like anterior or posterior communicating arteries recorded. In no cases were multiple anterior communicating arteries counted, although some were noted.

Findings

A valid breakdown of the general hospital cases into types of anomaly is not possible, but 11% of the 139 cases had anomalies of the types listed below. This is roughly comparable to the anomalies making up 17% of the cases reported by Alpers et al.[1] The general anomaly incidence in the psychiatric series of 256 cases was 35%. A breakdown of the 89 cases in the psychiatric group according to anomaly type follows:

(*a*) Fifty-two cases, 58%: A thread-like first segment of a single posterior cerebral artery with enlargement of the posterior communicating artery on the same side

(*b*) Nine cases, 10%: Like (*a*), but involving both sides symmetrically

(*c*) Five cases, 6%: Like (*a*), plus thread-like hypoplasia of the first segment of the anterior cerebral artery on the same side and enlargement of the anterior communicating artery

(*d*) Three cases, 3%: Like (*b*), plus hypoplasia of the first segment of the anterior cerebral artery on one side and enlargement of the anterior communicating artery

(*e*) Two cases, 2%: Like (*a*), with a double first segment of the anterior cerebral artery on the same side

(*f*) Eight cases, 9%: Hypoplasia of the first segment of one anterior cerebral artery with enlargement of the anterior communicating artery

(*g*) Three cases, 3%: A double first segment of one posterior cerebral artery

(*h*) Two cases, 2%: A double first segment of one anterior cerebral artery

(*i*) One case each, as follows: (1) hypoplasia of the entire right posterior cerebral artery; (2) duplication of the first segments of the anterior and posterior cerebral arteries on the same side; (3) hypoplasia of one anterior cerebral artery distal to an enlarged anterior communicating artery; (4) aneurysmal dilatation of the anterior communicating artery, and (5) hypoplasia of the end of the basilar artery with enlargement of both posterior communicating arteries and with hypoplasia of one anterior cerebral artery, as in (*f*)

The incidence of anomalies among various clinical diagnostic groupings showed some variation, as in the Table. "Other" includes manic-depressive, alcoholic, and post-traumatic psychoses; mental deficiency; epilepsy; Huntington's chorea, and remaining minor categories.

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Incidence of Anomalies According to Clinical Diagnosis

	Arterio-sclerotic	Senile	Schizo-phrenic	Other	Total
Anomaly	37	19	8	25	89
No anomaly	52	42	30	43	167
Total	89	61	38	68	256
% anomalies	42	31	21	37	35

No anomaly incidence correlations were found with respect to sex, alcoholism, hypertension, degree of psychosis, laterality of encephalomalacia, tumor, or brain trauma. There was no difference in incidence of encephalomalacia in groups with and without anomalies in the arteriosclerotic patients. Age at death of patients with and without anomalies followed a similar distribution, the average for both groups being 67 years. There was no preponderance of anomalies on one side or the other. No case of true absence of a circle component was noted.

In this same group of psychiatric patients there were six saccular aneurysms. Two of these, both on the proximal portion of the anterior cerebral artery, coexisted with anomalies, one as in (*a*), above, and one as in (*b*), above. This second one ruptured and was the cause of death. One of the other four aneurysms ruptured also. This was on the anterior communicating artery.

Comment

The difference in anomaly incidence between the arteriosclerotic and the schizophrenic groups and between the arteriosclerotic and the general hospital groups would seem to be real. The senile and "other" groups in the Table include many cases in which arteriosclerotic changes dominated the pathological brain changes. These are, therefore, somewhat intermediary groups. Generally the clinicopathological correlation of diagnosis as to degree of arteriosclerosis was good in the schizophrenic and arteriosclerotic patients, the latter having a great amount of severe sclerotic change and the former only occasional marked change. In patients with disabled mentation, then, there was a general tendency for those with arteriosclerotic changes to have a higher incidence of anomalies. This tendency is consistent with the hypothesis that arteriosclerosis and anomalies of the circle are additively detrimental to brain function. It must be remembered that this group is isolated from the general hospital patients in late life solely on the basis of disturbed behavior. That this selection results in a population with a high incidence of anomalies seems more than coincidental. Therefore, anomalies of the circle of Willis do contribute to psychiatric morbidity.

Summary

The incidence of anomalies of the circle of Willis thought to have effect on the circulation pattern was recorded in 139 nonpsychiatric and 256 psychiatric patients. The incidence in the former was 11% and in the latter 35%. In the psychiatric patients, arteriosclerotics had 42% anomalies, and schizophrenics had 21% anomalies. It is suggested that anomalies increase the incapacitating effect of arteriosclerotic brain disease.

Fairfield State Hospital.

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Long Survival After Unilateral Stab Wound of Medulla with Unusual Pyramidal Tract Distribution

JOSEPH A. LUHAN, M.D., Chicago

This paper is a report of a freakish and tragic experiment of nature, presenting us with an opportunity to study the effects of an incomplete hemisection of the medulla oblongata in man with long survival. The resulting patterns of secondary degeneration in the neuraxis form an interesting complement to the neuroanatomical studies of a bygone era at the dawn of this century, and tend to validate Dejerine's thesis [1] that there may be considerable variation in the distribution of the spinal pyramidal tracts. This becomes all the more intriguing because of the accumulating evidence and pronouncements [2-4] to the effect that our time-honored concepts of the pyramidal tract are in serious need of revision.

Report of a Case

On June 19, 1950, a 27-year-old waiter was repeatedly stabbed with a paring knife, one blow driving the blade through the foramen magnum into the right posterior cranial fossa. The blade was curled when withdrawn by the assailant. The victim of this assault was admitted to a hospital in a state of profound shock. Left hemopneumothorax had developed. Heroic emergency measures included plasma and blood transfusions, aspiration of blood and air from the left chest, tracheotomy to clear an airway, oxygen administration, tube feedings, administration of antibiotics, and use of a retention catheter.

After an initial critical period of clouded sensorium, the following salient neurological findings could be demonstrated. On the right side, there was paralysis or severe involvement of the motor and sensory 5th, 7th, 8th, 10th, and 12th cranial nerves and Horner's syndrome. The eyeballs could not be moved laterally, and there was spontaneous undulatory movement of the eyes, especially in the vertical axis. Pronounced cerebellar ataxia was present in the right extremities, marked by gross dyssynergy, dysmetria, adiadokokinesia, decomposition of movement, and tremor, which was not quite intentional in type. On the left side there was spastic hemiplegia, excluding the face, with exaggerated tendon reflexes, extensor toe signs, and absence of abdominal reflexes. Sensation below the face on the left side was greatly diminished to absent for the modalities of light touch, pain, temperature, vibration, and position sense of the fingers and toes. This was the neurological status when the patient was transferred about a month after injury to the service of Dr. Irving C. Sherman, at Cook County Hospital. Dr. Sherman made a diagnosis of combined extramedullary and intramedullary lesion of the right side of the medulla, the extramedullary component involving the cranial nerves on the right side. For several months the patient was profoundly depressed and almost succeeded in hanging himself, in spite of his neurological incapacities.

This case was presented by Drs. Sherman and Tentler at the meeting of the Chicago Neurological Society [5] on Feb. 13, 1951. At that time the patient had some very feeble power of movement of the left leg, which later disappeared. Because of abrasion of the insensitive cornea by the ataxic right hand, there followed perforating corneal ulcer, hypopyon, and blindness of the right eye. Trismus set in and persisted, so that an earlier observation of nystagmoid movement of the soft palate and some atrophy of the right half of the tongue could not be verified. The patient had severe swallowing difficulty throughout, frequently aspirated food or throat secretions, and suffered from bouts of pneumonitis. He remained hoarse; the vocal cords were never visualized.

Contracture of the left wrist developed, and the left extremities became atrophic, although the tendon reflexes remained hyperactive; pathological reflexes (Hoffmann and Babinski toe signs) persisted, and marked wrist and ankle clonus could be elicited on the left side. Unfortunately, during the last few years of this man's life no detailed sensory examination was recorded, and the relia-

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From the Stritch School of Medicine, Loyola University and Cook County Hospital.

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Fig. 1.—Section through the pontomedullary junction, stained by Klüver's method, showing path of the stab wound (dotted line) on the right side, penetrating the pyramid, continuing diagonally into the restiform body, and reaching the fourth ventricle.

bility of the observations would be open to question except that the general distribution of altered pain and touch sensibility remained unaltered.

The use of an indwelling catheter for nursing reasons led to periodic bouts of fever. The patient survived for over six years, dying on Aug. 20, 1956, from the effects of aspiration pneumonitis and sepsis.

Examination of Central Nervous System

Externally the formalin-fixed brain appeared relatively normal except that the ventral portions of the cerebellar hemispheres were somewhat shrunken and macerated, partly through artifact produced by the prosector. The large vessels at the base were thin-walled and patent. After the brain stem and cerebellum were severed through the midbrain, serial coronal slices through the brain proper revealed normal appearances. Serial cross-sectional slices through the brain stem and cerebellum, proceeding caudally, revealed nothing until the pontomedullary junction was reached. At this plane of section the right restiform body was largely missing from the medulla proper, and an area of rust-brown discoloration, about 4×8 mm. in surface dimensions, could be seen in the cerebellar course of this peduncle. The right pyramid appeared smaller and grayer than its

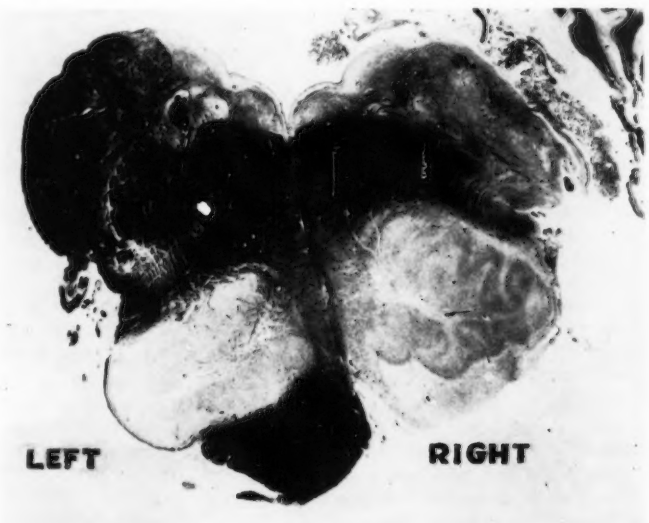


Fig. 2.—Section through the rostral medulla, stained by Weil's method for myelin, showing complete demyelination and marked atrophy of the right pyramid, degeneration of both inferior olives, replacement of the right restiform body by a glial scar, degeneration of ventral internal arcuate fibers, demyelination in both medial lemnisci except for the ventral part of the left medial fillet, and degeneration of the right tractus solitarius.

fellow. The spinal cord was macroscopically normal except in the cervical enlargement, where in cross sections the lateral white matter was smaller on the left side.

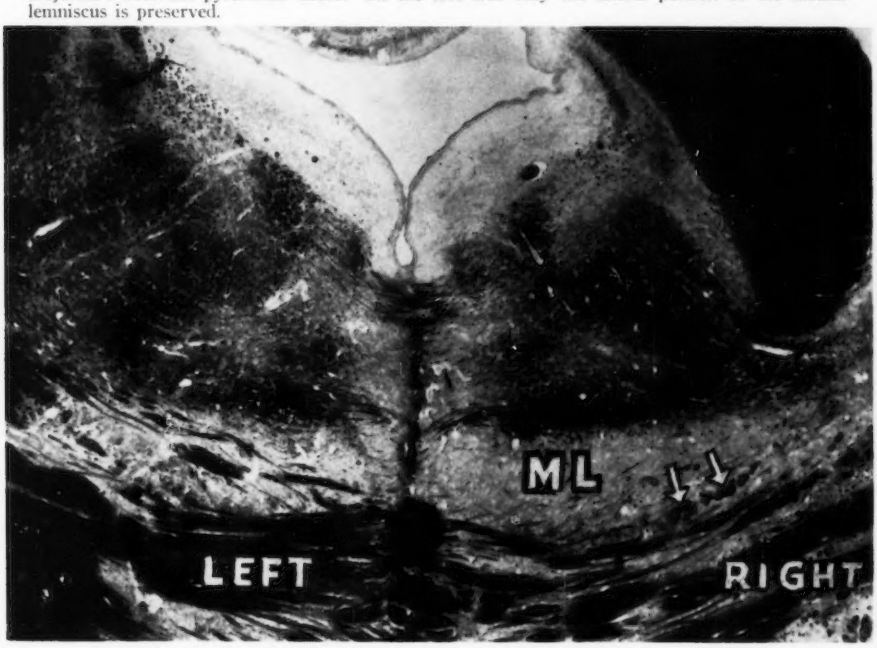
Sections through the pontomedullary junction (Fig. 1) revealed an old incisional scar of the right side penetrating the pyramid, continuing diagonally into the restiform body, virtually shearing off the stem of the eighth nerve, destroying the restiform body at this level, and reaching the fourth ventricle. Both inferior olivary bodies appeared degenerated.

Sections through the rostral medulla oblongata stained for myelin by the method of Weil (Fig. 2) revealed the right restiform body replaced by a glial scar, complete demyelination and atrophy of the right pyramid, degeneration and gliosis of both inferior olives, degeneration of ventral internal arcuate fibers, and demyelination of both medial lemnisci except for the most ventral portion of the left medial fillet. Silver stains disclosed complete axis-cylinder destruction in the right pyramid. The number of fibers in the medial longitudinal bundles and tectospinal tracts was reduced on both sides. Although the right 9th, 10th, and 12th nerve fibers within the medulla persisted, there was considerable reduction of cells in the right 10th and 12th nerve nuclei, and the right tractus solitarius had nearly disappeared. Besides the restiform body, the laterally situated vestibular nuclei, the parenchymal elements of the spinal tract and the nucleus of the fifth nerve, and Monakow's area were largely destroyed on the right. The large motor cells of the medial reticular formation were well preserved bilaterally; on the right the fiber bundles in this zone were somewhat sparse rostrally, but well developed caudally.

In sections through the decussation of the brachia conjunctiva stained for myelin one can observe that the lemnisci are degenerated on the right, whereas only part (the lateral third) of the medial lemniscus is present on the left. In sections through the rostral pons myelinated fiber bundles are present within the distribution of the demyelinated medial fillets corresponding to Dejerine's aberrant pyramidal fibers (Fig. 3).

A group of sections were all processed and stained alike, cut from the same block, and stained by Weil's method for myelin. At the pyramidal decussation, there are relatively little crossing of corticospinal fibers, and a completely degenerated pyramid on the right side (ipsilateral with respect to the stab wound); and the spinal tract and nucleus of the trigeminal nerve appears degenerated. At the first cervical level (Fig. 4) the degenerated right pyramid forms a large crescent;

Fig. 3.—Section through the rostral pons, stained by Weil's method, showing degeneration of the right medial lemniscus (*ML*) and revealing the presence of myelinated fiber bundles within the degenerated fillet (some of these bundles indicated by arrows), corresponding to Dejerine's aberrant pyramidal fibers. On the left side only the lateral portion of the medial lemniscus is preserved.



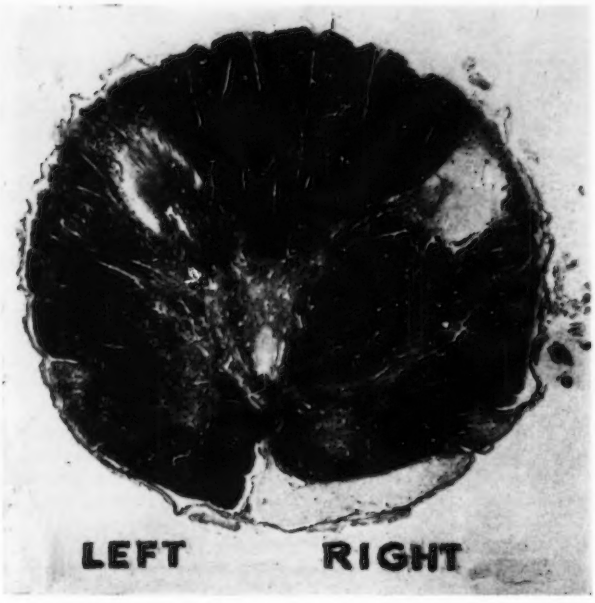


Fig. 4.—First cervical segment; Weil stain. The degenerated right pyramid forms a large crescent, while no discrete zone of demyelination is apparent in the opposite lateral white matter.

in the contralateral white matter no discrete area of demyelination of appreciable size may be seen. The fourth cervical segment presents a deformation artifact, but reveals much greater degeneration in the ipsilateral than in the contralateral white matter; however, the lateral white matter on the left is smaller than on the right. In the first lumbar segment there is some fiber outfall in the ventral funiculus and relatively little in the conventional zone of the crossed pyramidal tract. In the fifth lumbar segment the degeneration in the ventral funiculus can be readily seen under the microscope, but the degeneration in the lateral column is much less pronounced than what one ordinarily sees.

Fig. 5.—Sixth thoracic segment; Weil stain. The surface boundaries of the degenerated zone in the right ventral funiculus are indicated by the dotted line.

A section through the seventh cervical segment stained by the Pal-Kultschitzky variant of the Weigert method reveals a prominent zone of complete degeneration in the right ventral funiculus, which is difficult to show in a photograph. The area of ipsilateral, complete degeneration is 1.4 times that of the contralateral, incomplete lateral degenerated zone. However, the left lateral funiculus is distinctly smaller than the right.

The sixth thoracic segment stained by Weil's method shows a crescentic area of virtually complete degeneration in the ipsilateral column in cross-sectional area equal to the zone of incomplete degeneration in the contralateral pyramidal zone (Fig. 5).

Holzer-stained preparations for the demonstration of glial fibers at the various cord levels revealed an intensity of gliosis commensurate with the intensity and extent of the demyelination: pronounced in the degenerated zone of the ventral funiculus, slight in the zone of incomplete demyelination within the crossed funiculus. Silver stains for nerve fibers revealed practically complete loss of fibers in the nearly totally demyelinated zones, with preservation of numerous fibers in the area of the contralateral crossed pyramidal tract.

Comment

The bilateral degeneration of the inferior olives following unilateral wounding of the brain stem at the pontomedullary junction can be explained on the basis of injury to the ipsilateral central tegmental tract in the caudal pons and the crossed, retrograde degeneration of the contralateral olive after destruction of the restiform body.

The mechanism whereby the medial lemnisci underwent degeneration is not clear; part of the left medial fillet, as well as the right, was involved. However, in the fields of these degenerated tracts in the upper pons, well-preserved small bundles, corresponding to Dejerine's aberrant pyramidal fibers, could be seen in preparations stained for myelin; heretofore these have been demonstrated only by the Marchi method. Incidentally, in one of the Dejerines' cases [6] (Patient Rivaud), with infantile hemiplegia of 23 years' duration, there was some atrophy of the interolivary tracts without clinical sensory deficit.

The most striking feature with respect to descending degeneration in the cord of the present case was the greater degeneration in the region of the uncrossed pyramidal tract (in the ipsilateral ventral funiculus), in contrast to the smaller, and less complete, degeneration in the contralateral pyramidal tract. Questions arise (1) whether this represents merely an unusual variation, with the pyramidal fibers crossing to the other side in the course of their descent through the cord; (2) whether degeneration of other pathways, such as the vestibulospinal tract, contributed to the striking devastation in the ventral funiculus, and, finally, (3) whether, from preferential shrinkage of lateral pyramidal fibers, this tract may have become largely lost, in the sense that a large discrete zone of descending degeneration after the lapse of several years could no longer be demonstrated because the fibers simply disappeared, without reactive gliosis.

With respect to variations in the manner of crossing of the pyramidal tract, Lassek [7] writes that a lateral, or crossed, corticospinal tract, representing 85% to 90% of all fibers, descending the length of the spinal cord in primates, is taken for granted; but that variations occur in the manner in which the pyramidal tract crosses in the lower medulla. There may be complete crossing of both pyramids, or a complete decussation of one pyramid; both pyramids may remain uncrossed in the medulla but gradually cross in the white commissure of the cord. Verhaart and Kramer [8] described the case of a 28-year-old Chinese man with no crossing of the pyramid.

Lassek [7] remarks that a ventral, or direct, corticospinal pathway, forming 10% to 15% of the cord fibers, makes its definitive appearance in monkeys. In man it is described as terminating anywhere from the level of C 2 to the lumbosacral region, the average being in the midthoracic region.

The explanation of the vagaries of anatomical distribution of the direct pyramidal tract, as shown either by demyelination or by Marchi degeneration in human hemiplegic patients, became a matter of controversy in 1903 and 1904 between P. Marie and Guillain, on the one hand, and Monsieur

and Madame Dejerine, on the other. Marie and Guillain,[9] on the basis of Marchi preparations, concluded that following cerebral lesions the area of degeneration was small and extended through relatively few upper cord segments, whereas with pontine and peduncular lesions the degeneration in the ventral part of the cord on the side of the lesion was more extensive. In a lengthy paper on the direct pyramidal tract, published in 1904, based especially on degeneration revealed by the Weigert method, the Dejerines [1] concluded that the extent of degeneration in the anterior column of the cord in patients with hemiplegia depends not upon the site of the causal lesion but upon the caprices of decussation of the pyramidal tracts. They pointed out that the topography of the direct pyramidal tract varies with the levels of the cord. With a well-developed direct tract the degeneration occupies a crescent in the terminal oblongata. In the cervical enlargement it forms a large band from the anterior commissure to the sulcomarginal area. In the superior and middle thoracic regions, it shows a tendency to come to the front and assume the shape of a crescent. In the lower thoracic region the Marchi method shows the dwindling direct tract sinking posteriorly to the depth of the anterior column.

For comparison with the findings in the present case, Figure 6 shows one of the largest pyramidal tracts in the Weigert material of the Dejerines' series.

Essentially the same form of direct-pyramidal-tract degeneration revealed by the Marchi stain had been observed by Barnes [10] in 1901 in five cases of hemiplegia without brain stem lesions. In addition, Barnes described a tract of homolateral degenerated fibers near the periphery of the ventrolateral white matter, which some textbooks now refer to as Barnes' ventrolateral pyramidal tract. With reference to this controversy of Marie and Guillain *vs.* the Dejerines, a case in Weil and Lassek's series,[11] published a quarter of a century later, seems to substantiate the Dejerines' claims. This was a case of hemiplegia of one and one-half years' duration, with an unusually large crossed-pyramidal-tract degeneration without any direct pyramidal tract, in which the causative lesion was a pontile softening.

Weil and Lassek [11] studied preparations of the spinal cord stained for myelin, showing degeneration of the pyramidal tracts in 10 cases of hemiplegia. In four there was clear-cut degeneration of the anterior pyramidal tract; in four only scattered spots of demyelination were seen, and in two (20%) no degenerated fibers were found in the anterior funiculus. The direct pyramidal tract, when present, occupied a cross-sectional area in the cervical cord varying

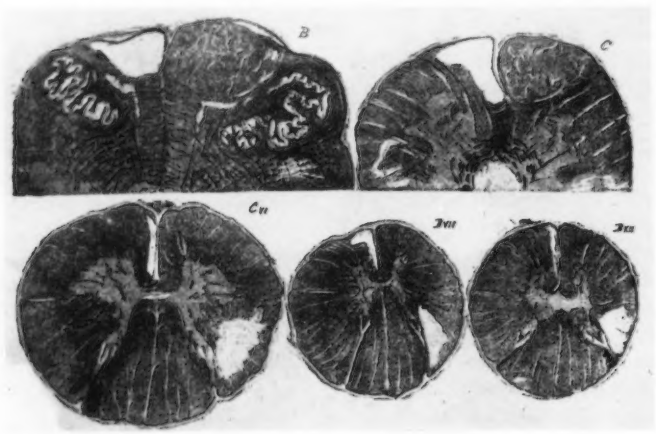


Fig. 6.—Figure 1 from the Dejerines' article,[1] referring to their case Pradel, showing a large direct pyramidal tract following a vast cortical lesion, as revealed by degeneration in Weigert-stained material.

from about 8% to 16% of that of the crossed tract. These authors pointed out that Flechsig, in studies of unmyelinated spinal pyramidal tract fibers in the fetus, found a similar ratio of 8% to 20%.

Lassek and Evans,[12] studying the spinal cord of a patient surviving 11 months after a hemispherectomy, found practically complete degeneration of the medullary pyramid, but many axons were still present in the crossed corticospinal tract, with fewer in the direct pyramidal area, and suggested that the ventral corticospinal tract may be important.

Whether degenerating fibers in descending pathways of brain-stem origin (particularly fibers of the ipsilateral vestibulospinal tract, from the anatomical evidence in this case) contributed to the fiber destruction in the anterior funiculus cannot be accurately assessed. However, the general form of the degenerated tract is much like that shown in the Dejerines' case (Pradel, Fig. 10), where the brain stem was spared. Von Bonin[13] writes that the vestibulospinal tract is a comparatively small bundle in man, and no clear description of it in man appears ever to have been given.

When we appraise the extent of secondary degeneration in Weigert- or Weil-stained material, the degree of condensation of fibers at varying cord levels, shrinkage from methods of processing the tissue, and atrophy of the degenerated area must be considered. With respect to atrophy, I have seen a mere sliver of gracile fasciculi at the first cervical level atrophied after many years in a case of syringomyelia, which in effect was almost a transverse lesion of the midthoracic cord. In another case, after a cerebral vascular accident which occurred 26 years before death, the shrinkage of the pyramidal tracts in the brain stem was striking. The question arises whether such atrophy may be differently advanced in the two spinal pyramidal pathways. In the case of the Dejerines' Patient Rivaud,[6] with infantile hemiplegia of 23 years' duration, the only degeneration seen in the spinal cord occurred in the ipsilateral ventral pyramidal region down to C 4, but the opposite lateral column was distinctly smaller than its fellow.

Summary

An unusual case of accidental incomplete hemisection of the medulla oblongata in man with long survival afforded opportunity to study various secondary degenerations within the brain stem and spinal cord. The descending degeneration in the cord revealed an unusually well-developed direct pyramidal tract, probably dependent on a vagary of crossing of the pyramidal fibers in the medulla.

29 E. Madison St. (2).

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An Arteriographic Study of Cerebrovascular Disease

FLETCHER H. McDOWELL, M.D.; ROBERT W. SCHICK, M.D.; WILLIAM FREDERICK, M.D., and HOWARD S. DUNBAR, M.D., New York

As part of a larger study of cerebrovascular disease, covering its diagnosis, natural history, and therapy with anticoagulants, this study was designed to evaluate the information to be gained and the risk involved in intracranial arteriography in patients with stroke. There is still difference of opinion concerning the safety of this procedure in the presence of degenerative cerebrovascular disease, as reported by several authors.[1-15] Emphasis was predominantly placed on the usefulness of the carotid arteriogram in helping to differentiate between cerebral thrombosis and intracerebral hemorrhage prior to anticoagulant therapy, especially when a record of the patient's history was nonexistent or incomplete. As the study progressed, the correlation between the severity of the clinically evident neurological defects and the nonfilling of the various cerebral arteries was also investigated.

Material and Method

The patients in this study were all admitted to the Second (Cornell) Neurological and Medical Division of Bellevue Hospital with the clinical diagnosis of "stroke." The term "stroke" as used here includes cerebral thrombosis, cerebral embolism, and intracerebral hemorrhage. It does not include spontaneous subarachnoid hemorrhage secondary to aneurysm, tumors, or arteriovenous anomalies. The number of patients in this study with intracerebral hemorrhage is less than might be expected, because many died before arteriography could be performed.

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From the Cornell Neurological and Neurosurgical Service, Bellevue Hospital.

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The common or internal carotid artery was usually punctured percutaneously. The vertebral angiography studies were all carried out percutaneously. Local anesthesia was usually employed, but general anesthesia with thiopental sodium was used if patients were restless or uncooperative. Bilateral studies were planned for all patients, but this procedure could not always be carried out, because of the precarious condition of some of the patients, failure to cannulate the second artery, restlessness of the patient following the first study, or local complications of the puncture in the neck.

Thirty-five per cent iodopyracet (Diodrast) was used for all studies except in two instances, when 50% diatrizoate sodium (Hypaque) was employed. No more than 10 ml. of the agent was used per injection, and usually two or three injections per artery were carried out.

Anteroposterior and lateral roentgenographic projections were obtained routinely with the x-ray film placed to include the bifurcation of the common carotid artery. A single exposure was taken with each injection. If an abnormality was observed, repeated injections with various exposures were made to confirm the findings, whenever possible.

Results

In 68 patients, with 69 separate episodes diagnosed clinically as "stroke," carotid arteriography was performed. There were 34 unilateral and 35 bilateral studies. Six patients had vertebral arteriography as well. The type and frequency of the various arteriographic abnormalities observed are listed in Table 1. An occlusive process was demonstrated 35 times in 32 patients and was inferred to be the cause of their neurological defects. More than one occlusion was demonstrated in three patients.

Middle Cerebral Artery.—This vessel was found to be occluded more frequently than any other artery, and occlusions were observed either in the main trunk or in one or more major branches in the arteriograms (Figs. 1-3) of 18 of 68 patients (26.4%).

TABLE 1.—*Arteriographic Findings in Patients*

Arteriographic Findings		Frequency Observed
Middle cerebral artery occlusion (including individual branches)		18
Internal carotid artery occlusion		11
Anterior cerebral artery occlusion		1
Basilar artery occlusion		1
Partial occlusion		4
Internal carotid	3	
Basilar	1	
Intracerebral hematoma		3
Nonvascular lesions		3
Nonocclusive arterial abnormalities		20
Normal		7
Unsatisfactory studies		4

Internal Carotid Artery.—Internal carotid artery occlusion was found in 11 of 61 patients (18%). This artery was occluded, with one exception, at or near its origin from the common carotid, and in the one exception, in the intracranial portion of the artery just before the bifurcation. The high incidence of occlusion in the artery has been noted before [8,14] and again points up this area as a major source of cerebral damage in patients with strokes.

Anterior Cerebral Artery.—The anterior cerebral artery was found to be occluded distal to the junction with the anterior communicating artery only once in this series. The rarity of occlusion in this artery has been observed in previous studies.[2,8] An occlusion of the anterior cerebral artery between its origin and the anterior communicating artery could easily occur without symptoms, as this artery frequently fills adequately from both internal carotid arteries. Nonfilling from one side with adequate filling from the opposite side occurred in several patients in this series, but in no instance could this finding be correlated with the patient's clinical findings.

Partial Occlusion.—Partial occlusion of the carotid or vertebral artery circuit was observed four times (Fig. 4). Such a diagnosis was made when a gross localized, well-defined filling defect was seen on the arteriogram with or without evident impairment of filling beyond the defect.

Vertebrobasilar Occlusion.—Vertebrobasilar occlusion was found only once in this series, and this incidence is similar to that reported by others.[2,8] Although both carotid and vertebral angiograms were obtained on only a few patients, it is considered unlikely that many occlusions in the vertebrobasilar system have been missed, because of the frequency of findings in the carotid arterial system which could easily account for the clinical evidence of brain damage. This does not eliminate the occurrence of atherosclerotic disease in this area as a contributing cause of symptoms.

Intracerebral Hematoma.—Three patients were found to have an intracerebral

Fig. 1.—Complete right middle cerebral artery occlusion.

Fig. 2.—Occlusion of a branch or branches of the left middle cerebral artery.

Figure 3

Fig. 3.—Right carotid angiogram of the patient in Figure 2, showing complete filling.

Figure 4

Fig. 4.—Partial occlusion of the left internal carotid artery, showing two large well-defined filling defects opposite the arrows.

hematoma by arteriography. In all of these patients an intracerebral hematoma was suspected on clinical grounds, but the diagnosis was not established with certainty before arteriography. There was no instance in the series in which arteriography was helpful in distinguishing a cerebral thrombosis from an intracerebral hemorrhage prior to anticoagulant therapy when the bedside examination did not strongly suggest one in favor of the other.

Nonvascular Lesion.—Three patients clinically diagnosed as having strokes were found by arteriography to have nonvascular lesions. Two had subdural hematoma, and one had a tumor. This would indicate that the clinical diagnosis of stroke may be inaccurate at least 5% of the time. It further points out that a diagnosis made without an adequate history, as was often the case in this series, is difficult and suspect.

Nonocclusive Arterial Disease.—Nineteen patients had arteriograms which showed arterial abnormalities but failed to show clear evidence of arterial occlusion or displacement. The presence of such a large number of these patients in the group showing no clear evidence of occlusion can be attributed in part to the difficulty in interpreting arteriograms and in visualizing occlusions beyond the second arterial branching, especially in the middle cerebral artery. Even with the opposite side for comparison, a clear visualization and identification of occlusion in the smaller branches of cerebral arteries is seldom possible.

Other associated nonocclusive vascular abnormalities were present in all of these 20 patients. The arterial abnormalities usually seen were tortuosity of the larger arteries, small irregular defects in the arterial wall, and irregular dilatation or constriction of the internal carotid artery or its branches. These abnormalities are commonly considered to be evidence of atherosclerosis. Another abnormality which was often observed, but the significance of which is not clear, was inability of the smaller arteries to fill or their filling only after a delay in which venous

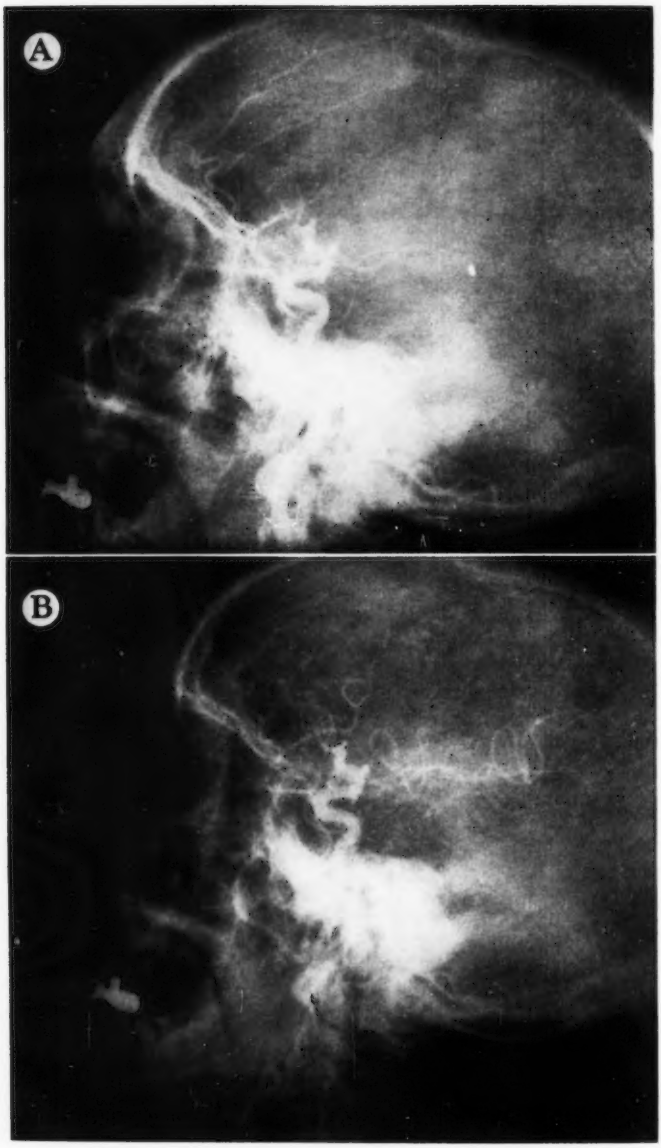

Fig. 5.—Right carotid arteriograms: early phase (*A*) and late phase (*B*), showing "short filling" in the branches of the middle cerebral artery. The x-ray in *B* was taken two to three seconds later, following injection, than in *A*.

filling could normally be demonstrated (Fig. 5). This finding had been designated as "short filling" by Riishede [8] and is taken as indicating an abnormality in cerebral circulation of sufficient magnitude to account for cerebral dysfunction. Such findings are often helpful in differential diagnosis but do not afford a clear explanation of the cause of the resultant central nervous system dysfunction.

Clinical Correlation

In an effort to correlate the clinical with the arteriographic findings, all of the strokes were graded as mild, moderate, or severe. Mild strokes were characterized by

TABLE 2.—*Arteriographic and Clinical Correlation in Sixty-One Patients*

Arteriographic Findings	Severity of Neurological Defect		
	Mild	Moderate	Severe
Middle cerebral artery occlusion (at its origin)	0	0	7
Middle cerebral artery occlusion (in a branch)	0	5	5
Internal carotid artery occlusion	1	6	3
Anterior cerebral artery occlusion	0	0	1
Basilar artery occlusion	0	0	1
Partial occlusion	3	0	0
Nonocclusive arterial abnormalities	3	13	3
Norma	5	1	1
Intracerebral hematoma	0	0	3

rapidly clearing motility and sensory disturbances with little or no residual dysfunction and without change in the level of consciousness. Moderate strokes were characterized by clearly evident hemiparesis or hemisensory defects with some clearing but with obvious residual dysfunction. A severe stroke was characterized by complete hemiplegia with little or no recovery and accompanied by severe disturbances in the level of consciousness. In Table 2 the severity of 62 strokes occurring in 61 patients has been indicated with the arteriographic findings. It can be seen that all patients, except one, with clear radiographic evidence of occlusion of a cerebral artery clinically had a moderate or severe stroke. Seven patients with occlusion of the middle cerebral artery at its origin are all found in the severe category. With occlusion of a branch or branches of the middle cerebral artery, the patients are equally divided between the moderate and the severe category. In the group of 10 patients with occlusions of the internal carotid artery, the majority are found in the moderate category, 3 in the severe, and 1 in the mild, category. The three patients in whom partial occlusion was the only significant arteriographic abnormality had mild strokes. Patients with nonocclusive cerebral arterial abnormalities tended to have moderate to severe strokes, while those with normal cerebral arteriograms had mainly mild strokes.

The three patients with intracerebral hematomata all had severe neurological defects.

Comment

There is no difficulty in correlating the clinical and arteriographic findings when an arterial occlusion is clearly demonstrable, as in middle cerebral artery occlusion. It is of interest, that in general, patients with internal carotid artery occlusion had less severe clinical neurological defects than those with middle cerebral artery occlusions. There were three exceptions to this observation: The first had an associated contralateral occlusion of the middle cerebral artery; the second had had a previous stroke, and the third had an intracranial occlusion. The difference can be accounted for by the availability of collateral circulation when the internal carotid artery is occluded at or near its origin, and the lack of such circulation when the middle cerebral artery is occluded.

Twenty of the patients in this study with moderate or severe clinical defects, however, failed to show any correlation, because of the absence of demonstrable occlusions. Nevertheless, their arteriograms were not considered normal; and if one broadens the usually accepted criteria of arteriographic abnormality and includes those findings mentioned, then the correlation in these patients becomes much higher. This study suggests that these arteriographic findings are indicative of nonocclusive degenerative cerebrovascular disease of sufficient degree to account for the clinical findings seen in patients without major occlusions.

Of the seven patients who had normal arteriograms, five had strokes classed as mild, one as moderate and one as severe. In the patient with the moderate stroke it was difficult to determine how much of his neurological deficit was recently acquired, as he had had syringomelia for several years before his stroke. One patient in this group with a severe stroke had a normal arterio-

TABLE 3.—*Age and Incidence of Complications*

Age Groups	No. of Patients	No. with Complications	
		No.	%
30-39	3	0	0
40-49	6	0	0
50-59	17	1	5.9
60-69	30	7	23.3
70-79	11	5	45
80+	1	1	100

TABLE 4.—*Relation of Patient Prior to Angiography and Complications*

State	No. of Patients	Complications	
		No.	%
Patients in coma or stupor, or worsening	13	13 (11 deaths)	100
Patients alert with stable clinical status	55	1	2

gram. The combination of a normal arteriogram and clinical evidence of marked neurological dysfunction is difficult to explain, especially in a patient who has demonstrably patent internal carotid arteries. A prolonged hypotensive episode occurring in a patient with atherosclerotic changes in cerebral vessels could account for such a combination, but at best such an explanation is not wholly satisfactory.

Complications

The incidence of local complications associated with arterial puncture is no different for patients with cerebrovascular disease than for any other group. Fourteen of the patients, after arteriography, showed an increase in the severity of their hemiplegia or a decrease in their level of consciousness or died.

Age appeared to have a definite relation to the occurrence of complications in that the average age of those patients with complications was 67, as compared with the average age of 60 for the whole group. As can be seen in Table 3, the percentage of complications rises with increasing age, reaching 45% for the 70-80-year-old group.

Associated illness other than cerebrovascular disease appeared to influence the frequency of complications, as all of the patients with serious and permanent complications had hypertension, diabetes, or heart disease.

Complications appear to be clearly related to the clinical state of the patient at the time of arteriography. Fourteen patients in this series became worse or died in a few minutes to 140 days following arteriography. Seven of these had been in coma for hours or days and had shown progressive worsening of their neurological status prior to the procedure. Six were stuporous and had some worsening of their neurological defects prior to arteriography. One patient who was alert and who was showing improvement before arteriography was transiently worse afterward.

As can be seen in Table 4, these patients have been divided into two groups for the purpose of deriving a clearer picture of the frequency of complications.

TABLE 5.—*Complications Following Intracranial Angiography*

Author	Year Reported	All Patients			Patients with Cerebrovascular Disease		
		No. Patients	No. Complications	% Complications	No. Patients	No. Complications	% Complications
Dunsmore	1951	108	7	6.4	12	2	16.6
Abbott	1952	150	9	6.0	17	3	17.6
Latimer	1952	215	3	1.4	72	2	2.6
Rowbotham	1953	430	15	3.4	22	2	9.0
Decker	1954	--	--	--	97	0	0
Perese	1954	200	10	5.0	19	4	21.0
Sedzimer	1955	169	0	0	14	0	0
Rilshede	1957	--	--	--	100	0	0
Coddon and Krieger	1958	483	109	22.0	33	6	18
Present series	1958	--	--	--	68	14	20

The first group were those in coma or severely obtunded, with rapidly worsening neurological status. All of the deaths and serious complications occurred in this group of patients. Those patients who exhibited a stable or improving neurological status had no serious or permanent complications following arteriography. One had a mild transient hemiparesis following the procedure.

The reported incidence of complications, fatalities, permanent hemiplegias, or other defects following arteriography varies from none to 22%.[2,3,8,9,15] As can be seen in Table 5, the incidence of complications in this series is higher than that reported by several authors.[1-5] Riishede[8] and Decker[2] reporting on series of patients with cerebrovascular disease of comparable size, report no permanent complications, but they do not indicate whether their patients were acutely or chronically ill.

It is usually difficult to determine clearly from personal experience and from the reported experience of others when complications can be directly attributed to angiography. We believe that it is clear that the deaths and severe complications in this study following arteriography are related to the clinical state of the patient; that is to say, arteriography is more likely to be associated with complications in the patient who is stuporous or comatose and shows evidence of worsening following the onset of his stroke. This has also been pointed out by Coddon and Krieger.[15] There was only one complication in patients who were improving or whose neurological findings were stable.

We believe that it will never be possible to give an accurate estimate of the incidence of complications of arteriography when it is carried out in comatose, seriously ill, or moribund patients, because most of the disorders for which arteriography is performed carry a high morbidity and mortality incidence. Any statement of the incidence of complications and mortality following arteriography will be a mixture of the incidence of complications of the procedure and the disease process itself. This is especially so in all types of cerebrovascular disease in which the morbidity and mortality rates are high even in uncomplicated situations, and extraordinarily high when associated with prolonged coma and continuous worsening.

Summary and Conclusions

Cerebral angiographic studies were performed on 68 patients with 69 strokes. They revealed that the artery most frequently occluded was the middle cerebral (18 of 68 patients, or 26.4%), and the next most frequent, the internal carotid (11 of 68 patients, or 16.0%).

Angiograms were not helpful in distinguishing intracerebral hemorrhage from cerebral thrombosis when the clinical examination did not help make this distinction.

The majority (70%) of the patients in this series with severe neurological defects were found to have an occlusion in a major cerebral artery.

Angiography is not advisable or helpful in the diagnosis of the usual patient with an adequate history and clinical findings suggesting stroke. It may be helpful in clarifying the diagnosis in patients with an inadequate history or no available history. In such patients arteriography may aid in eliminating the possibilities of subdural hematoma, intracerebral hematoma, and brain tumor.

Carotid arteriography should not be performed in patients with cerebrovascular disease if they are in coma or stupor or if their clinical state is steadily worsening. The risk of complications is least when the patient is improving or when his clinical state has stabilized.

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Studies on Cerebral Oxygenation During Induced Hypotension

ROBERT L. McLAURIN, M.D.; JOHN W. DEVANNEY, M.D.; EUGENE B. ELAM, M.D., and RICHARD B. BUDDE, M.D., Cincinnati

Although induced hypotension is being employed less frequently now than previously, the method still has clinical value as an adjunct in the surgical management of certain vascular and neoplastic lesions. The present study was undertaken in an attempt to elucidate by a new technique the cerebral hemodynamics associated with induced hypotension. Previous literature concerning hypotension contains numerous references to a "safe" or "critical" level of blood pressure below which cerebral nutrition is impaired. The basis for these terms, however, has remained obscure because of difficulty encountered in measuring rapidly occurring or minor variations in cerebral oxygenation. The present work is an effort to determine whether there does exist a critical level of blood pressure for maintenance of adequate cerebral oxygenation. In addition, a comparison is made between the effect of chemical-induced hypotension and the effect resulting from blood loss, since each method has been advocated on certain theoretical or experimental grounds.

Prior to introduction of the nitrous oxide technique for measuring cerebral blood flow [12] there was no satisfactory means of evaluating intracranial hemodynamics. The method provided a valuable investigative tool, despite certain limitations of the technique. Beginning in 1942 with the work of Davies and Brink,[5] and elaborated recently by Meyer, Fang, and Denny-Brown,[15] electropolarography has been applied to the problem by means of acute experiments. This technique utilizes the principle that reduction of oxygen occurring at a platinum electrode carrying a certain electrical potential results in a measurable flow of current proportional to the amount of oxygen available. The feasibility and apparent reliability of chronically implanted electrodes have been described previously,[3,14] and the present work is an application of this technique to animals undergoing induced hypotension.

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From the Division of Neurosurgery, Department of Surgery, University of Cincinnati College of Medicine.

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Method

Experiments were carried out on 18 mongrel dogs. The methods of electrode implantation and electrical recording have been previously described. Experiments were performed at intervals following electrode implantation varying from 2 to 44 days. Repeated experiments were carried out on several animals to determine whether there was consistency in the pattern of response to hypotension.

For each experiment the animal was anesthetized with pentobarbital (Nembutal). An intratracheal tube was inserted and constant respiratory rate (14 per minute) and volume (variation between 250 and 350 cc. per cycle, depending on animal size) maintained by means of a nonrebreathing respirator. The femoral artery was catheterized for direct measurement of blood pressure and the systolic pressure recorded at frequent intervals during the observation. The polarographic base line during air breathing was established after stabilization. Deflections were noted in response to 100%-oxygen breathing and then in response to anoxia induced by use of either 100% helium or 100% nitrous oxide. These values served as confirmation of the responsiveness of the electrode to changing oxygen availability and also as points of comparison for the magnitude of subsequent changes under experimental conditions. It should be noted that the polarographic change between air breathing and 100%-oxygen breathing is sev-

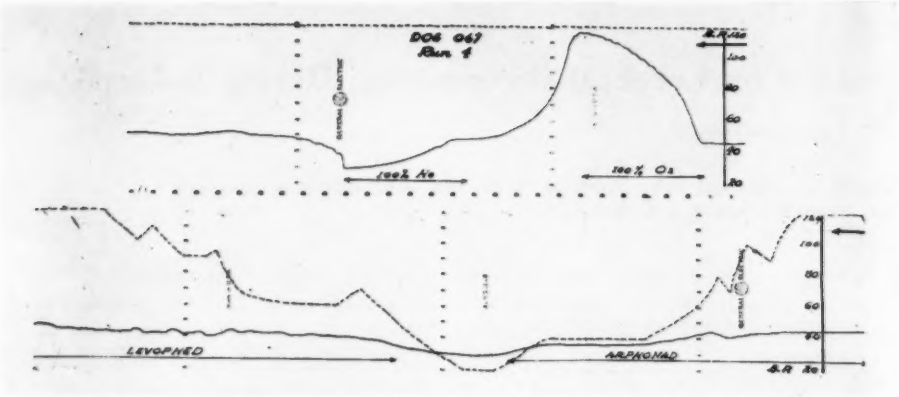


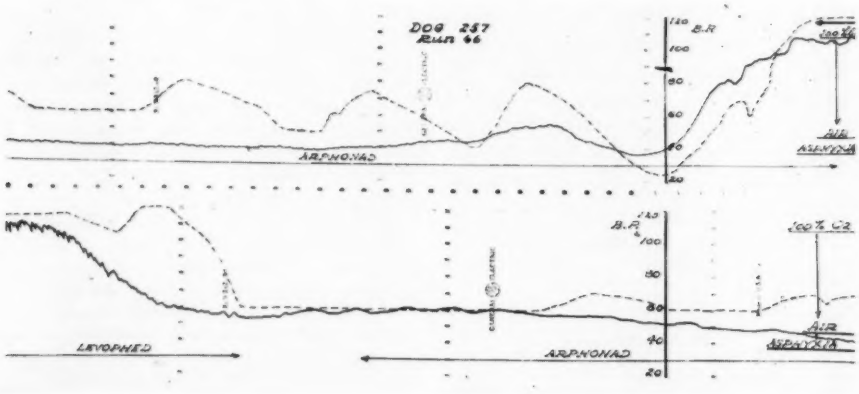
Fig. 1.—Polarographic response to 100%-oxygen breathing and to anoxia. Note that all reproductions of polarograms read from right to left. Subdivisions on graph paper represent one-second intervals. The magnitude of the response to excess O_2 in comparison with that during anoxia is well shown and was characteristic in all experiments. The lower polarogram shows decline of O_2 availability in response to lowering of blood pressure. Broken line represents systolic blood pressure.

eral times greater in an opposite direction than the change between air breathing and asphyxia (Fig. 1). Because of the near-saturation of hemoglobin with oxygen during air breathing, the marked increase in polarographic reading during 100%-oxygen breathing must represent availability of large amounts of oxygen in solution, rather than as oxyhemoglobin.

In this study, 46 experiments in 13 animals were carried out by inducing hypotension with intravenous trimethaphan (Arfonad), a thiophanium derivative. This was given as a dilute solution, and the rate of administration was used to control the fall in blood pressure. Levarterenol (Levophed) was also administered to counteract the effect of trimethaphan when it was desired to return the blood pressure to normal levels.

Eleven experiments were done by inducing hypotension by partial exsanguination. This was accomplished by bleeding from a femoral artery into a reservoir from which the blood could be reinfused. Removal of blood was accomplished during intervals varying from 8 to 23 minutes, and the average amount of blood removed was 400 cc.

Fig. 2.—Linear response of O_2 availability to lowering of blood pressure by trimethaphan (Arfonad). Levels of polarographic response on air breathing, 100%-oxygen breathing, and asphyxia are shown at the upper right of this and subsequent polarograms. The O_2 availability declines parallel to lowering of blood pressure and also rises when blood pressure is elevated by levarterenol (Levophed).



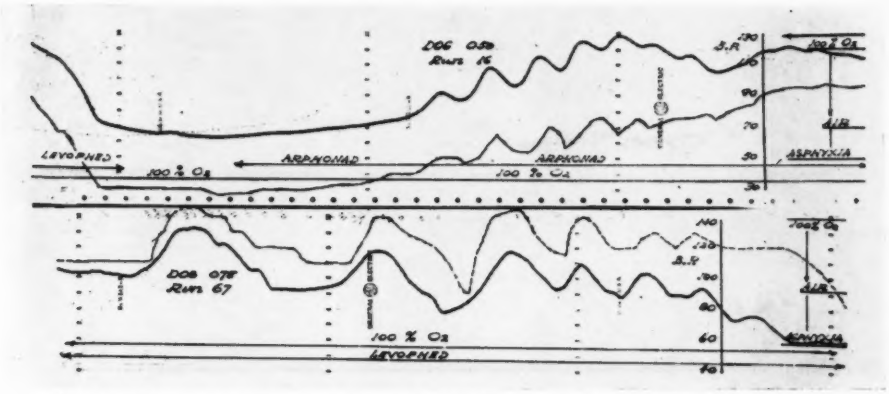
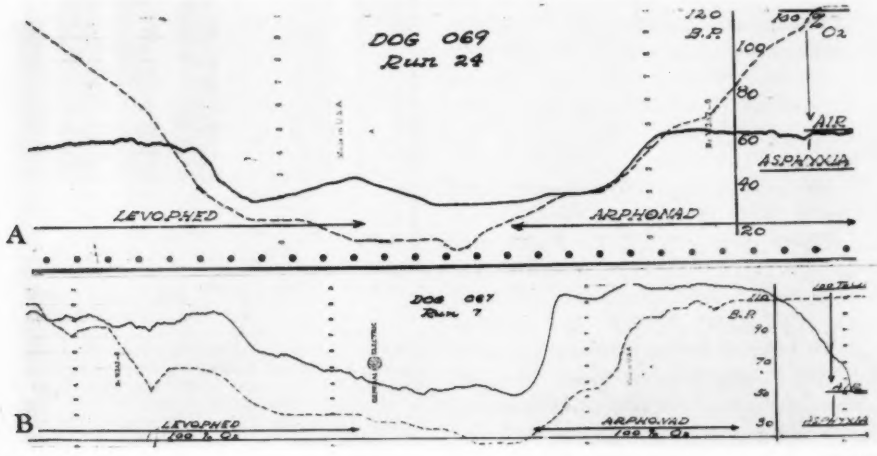


Fig. 3.—Linear response of polarogram to blood pressure changes. These are experiments on different animals. In the upper part, the lower line represents blood pressure; in the lower, the upper (broken) line represents blood pressure. The marked fluctuations of O_2 availability which accompany blood pressure swings are shown.

Results

Two patterns of response were noted during chemical-induced hypotension. The majority of experiments (30 out of 46) showed a linear fall in the available cerebral oxygen (ACO), which was parallel to the fall in blood pressure (Figs. 1 and 2). Decline of ACO began simultaneously with the fall of blood pressure from normotensive levels. Although there was considerable difficulty in controlling the rate of fall of blood pressure because of variable susceptibility of the animals to trimethaphan, there was no apparent difference in response to slow or rapid pressure decline. The high degree of correlation between ACO and blood pressure was strikingly noted in several experiments, in which rather wide fluctuations in pressure occurred (Fig. 3). In those animals showing a linear fall of ACO, restoration of the pressure to a normal level resulted in a linear and parallel eleva-

Fig. 4.—Compensatory response of polarogram to blood pressure changes. *A*, O_2 availability maintained until blood pressure lowered to about 65 mm. Hg. Reverse response noted on blood pressure elevation. *B*, O_2 availability maintained until blood pressure lowered to 50 mm. Hg, with sudden precipitous lowering of O_2 availability.



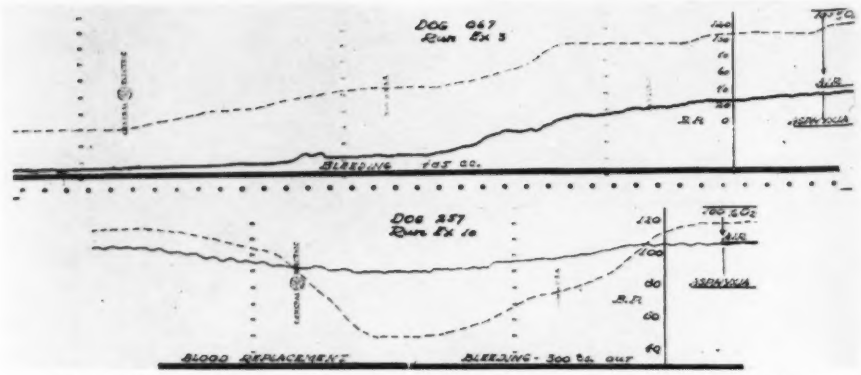


Fig. 5.—Two experiments on exsanguination, showing linear decline of O_2 availability to hypotension produced by bleeding. There is noted no compensatory maintenance of cerebral oxygenation in the face of falling blood pressure. Lower graph shows linear rise of O_2 availability when blood was replaced.

tion of ACO. This occurred irrespective of the length of time of hypotension up to periods of 35 minutes.

Sixteen experiments, performed on six animals, showed partial compensation of ACO to decreasing blood pressure. In this group blood pressure dropped significantly below the normal (110 to 140 mm. Hg systolic) before a fall was noted in ACO. As will be discussed subsequently, it is assumed that some mechanism is operating to maintain the cerebral blood flow constant despite a fall of systemic blood pressure. The level of pressure at which compensation terminated varied between 45 and 100 mm. Hg, with an average of 72 mm. Hg. When compensatory ability was lost, decline of ACO was rather rapid (Fig. 4). Of the six animals showing compensated polarographic responses, five demonstrated linear reaction on subsequent experiments, indicating no consistency of reaction in a particular animal.

Response to exsanguination was a linear decline in all 11 experiments (Fig. 5). In this respect they were similar to the majority of trimethaphan experiments. Blood pressure reduction was accomplished more slowly by bleeding than by chemical blockade. Return to normotension on blood replacement was likewise linear in configuration. No compensatory maintenance of ACO was noted in these experiments.

From a practical standpoint, the relationship of ACO during hypotension to that recorded under normotensive conditions while the animal was breathing air seemed to be of fundamental importance. While cerebral function may be adequately maintained with

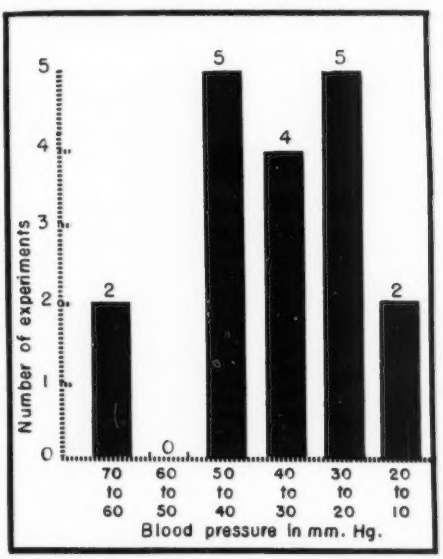


Fig. 6.—Analysis of polarographic curves obtained in 18 experiments using trimethaphan (Arfonad). The blood pressure at which the curve of O_2 availability in animals breathing 100% oxygen crossed the initial base line obtained in the air-breathing normotensive animal was determined. The block graph demonstrates that in most animals normal O_2 availability was present until pressure was lowered to 20-50 mm. Hg.

partial reduction of normal cerebral oxygen supply, a safe level of hypotension should be one which allows the same degree of oxygenation as that which is present during normal blood pressure and respiratory intake. The experiments were analyzed to determine at what level of pressure during 100% oxygen breathing the ACO was equal to the available cerebral oxygen in the normotensive air-breathing animal. Since the polarographic method cannot be interpreted in quantitative terms, it is necessary to compare changes in ACO with the resting state in each experiment. Thus, each animal serves as his own control for these observations.

Figure 6 shows the results of analysis of 18 experiments in trimethaphan-induced hypotension. The majority of animals were able to maintain an adequate cerebral oxygenation to levels of less than 50 mm. Hg. Most of the polarographic recordings crossed the air-base-line between 20 and 50 mm. Hg, while a few did not reach this point with pressure as low as 15 mm. Hg in the femoral artery. The animals were maintained in the horizontal position during these experiments, and it may be assumed that the intravascular pressure in the carotid vessels was comparable to that recorded from the femoral artery. It is noteworthy that there is marked variation among the animals tested and that the "safe" level of pressure is nearly always less than 50 mm. Hg.

Nearly all dogs have been autopsied and the findings at the site of the implanted electrodes found to correspond closely with those described by Collias and Manuelidis.[4] Because of the similarity of the curves obtained at various stages of chronicity, we concluded that the developing glial scar about the electrode tip does not affect the electrical results within the time limit (44 days) of our experiments. It is possible that the membrane may compare with the dialyzing membrane which has been used to sheath electrodes in other methods.

Comment

The relatively large demand of the brain for oxygen renders it particularly susceptible to variations in its blood supply. We have assumed that the oxygen available to our electrode is also available to the brain cells. It is recognized that oxygen is only one of the substances necessary for cerebral metabolism, but there is no evidence so far that other substrates are in critical demand during hypotension.

Another assumption which is believed valid is that available cerebral oxygen (ACO) is controlled by three factors: (1) blood supply to the brain, (2) O_2 saturation of the blood being delivered, and (3) rate of metabolic consumption of the delivered O_2. In the present experiments there was probably no significant variation occurring in the cerebral metabolic rate under anesthesia. Since oxygenation of the blood was controlled at all times, it is believed that the polarographic changes represent variations in the cerebral blood flow. This would hold true only as long as the inspired gas remained constant.

The linearity of the polarographic response to progressive lowering of blood pressure, observed in most experiments, arouses considerable interest, as it contrasts with certain previous investigations. Hafkenschiel, Crumpton and Moyer,[9] using the nitrous oxide technique, demonstrated no change in cerebral blood flow in normotensive humans when the mean blood pressure was reduced an average of 17% by means of dihydroergocornine, a drug with both vasodilating and adrenergic-blocking properties. The same ability to compensate for moderate degrees of hypotension was noted in hypertensive patients, and the authors concluded that the drug must have a specific cerebral vasodilating effect.[10] Since our observations show a drop in cerebral blood flow beginning with the initial decrease of blood pressure in two-thirds of trimethaphan experiments, we must conclude that the drug does not work in most animals to decrease cerebral vascular resistance in compensation for lowered blood pressure. If cerebral vascular resistance remains constant, cerebral blood flow will necessarily vary directly with blood pressure.

It is apparent, therefore, that in most experiments there was no variation in cerebral vascular resistance.

There are several possible explanations for the lack of changes in cerebral vasomotor tone. Kety and Schmidt [13] have shown that increased oxygen supply to the brain will effect a reduction in cerebral blood flow. It may be postulated that in the presence of a supernormal supply of oxygen, as was present in our animals breathing 100% oxygen, the cerebral vascular resistance was maintained at a constant maximal level, at least until such a degree of hypotension was reached that the normal O_2 supply was no longer maintained. This postulate is difficult to accept because no leveling of the polarogram was noted when the O_2 supply had dropped to the air-base-line, and animals which did not have excessive oxygen intake showed a similar configuration and rate of decline of available cerebral oxygen.

A second possible explanation of the linear response concerns the depth of anesthesia. Observations of most previous investigators who noted cerebrovascular compensation have been carried out on humans who were under no anesthesia. It is noteworthy, however, that Clark, Misrahy, and Fox,[3] using polarographic technique, found no effect from pentobarbital, and this was true in our previous observations.[14] Nevertheless, the possible paralyzing effect of anesthesia on cerebrovascular compensation must be recognized. Indeed, if the depth of anesthesia is significant, variations in anesthetic level may explain the fact that one-third of our animals were able to compensate for chemical-induced hypotension. Of considerable interest in this regard are the observations of Ingvar and Söderberg,[11] who studied cerebral blood flow in cats by cannulating the sagittal sinus. The method possesses the advantage of detecting rapid and small fluctuations in blood flow. They noted that during light barbiturate anesthesia the blood flow was not correlated with blood pressure, while in deep anesthesia blood flow was directly related to blood pressure, presumably owing to constancy of the vascular resistance.

A third possibility lies in the rapidity of lowering of blood pressure. Fazekas, Albert, and Alman [6] have demonstrated progressive vasodilatation of the cerebral vessel as hypotension, induced by trimethaphan, was maintained. Because of difficulty in controlling trimethaphan response in dogs, the rate of lowering blood pressure in our experiments was usually fairly rapid, over periods of about five minutes. The progressive compensation might explain the difference between linear and compensated polarographic responses to hypotension if it may be postulated that the linear type of reaction indicates inability for vasodilatation to proceed rapidly enough to maintain a constant blood flow. The rapidity of blood pressure fall was the same in the two types of response. Also, the linear type of reaction was seen during exsanguination hypotension, and this occurred much more slowly than when trimethaphan was used. It would appear, therefore, that delay of vasodilatation would not account for the linear reaction.

The final possible explanation lies in the matter of species difference. There may be considerable difference in the vasomotor reaction in humans in comparison with lower vertebrates. While we are not aware of any studies similar to ours using chemical blockade alone, the recent work of Bloor, Floyd, Hall, and Reynolds [2] on hypotension from controlled blood loss in dogs must be mentioned, as definite compensation was noted until the mean blood pressure was reduced to approximately 50% of its initial level.

None of the above explanations can be supported by the present experiments, although depth of anesthesia appears to be the most logical on the basis of evidence available. The variability of response in a given animal during repeated experiments would support this explanation.

From the standpoint of clinical application, the experimental evidence indicates that there is no valid "critical" level of blood

pressure necessary to support cerebral function. If the "safe" level is taken as that which maintains the normal supply of oxygen (Fig. 5), our results indicate that this usually falls between 30 and 50 mm. Hg. The average blood pressure above which trimethaphan-treated animals were able to maintain normal cerebral oxygen availability was 38 mm. Hg in those animals showing a linear reaction to hypotension, and 26 mm. Hg in those showing some degree of compensatory maintenance of cerebral oxygenation. This would indicate that in the latter group there is some protection in addition to that afforded by the trimethaphan. Again, the marked individual variation is noted, and the danger of applying a statistical average to the individual case is apparent.

Nearly all previous studies concerning a "safe" level of blood pressure have been performed on unanesthetized subjects. It is hazardous to apply the observations to clinical situations in which cerebral hemodynamics may be altered by the anesthesia. Moreover, the cerebral oxygen consumption is significantly reduced under barbiturate anesthesia.

The concept of a "critical" level of blood pressure probably should be discarded. Griffiths and Gillies [8] have indicated that capillary circulation is insured if pressure is slightly in excess of venous and colloid osmotic pressure of the plasma, about 32 mm. Hg. All pressure in excess of this is used to overcome peripheral resistance; and if there is no resistance excess, pressure is not necessary. Clinical support was offered in the work of Finnerty, Guillaudeu, and Fazekas,[7] who found that the "critical" level of blood pressure, as judged by the appearance of syncope, varied from 34 to 100 mm. Hg. The crucial factor was blood flow rather than pressure; and when blood flow was reduced to 60% of normal, syncope occurred. It is quite possible that the linear configuration of the majority of our experiments using chemical blockade is simply a reflection of the decreasing cardiac output due to trimethaphan, rather than an expression of any tendency to divert the blood supply to areas other than the brain.

Evidence obtained from these experiments does not indicate any preferability between the hypotension induced by chemical blockade and that due to exsanguination. It must be noted that these are two entirely separate conditions, the common denominator being a low arterial blood pressure. In one there is no decrease of blood volume, and hence no vasoconstriction; this leads to better tissue perfusion. Proponents of the clinical use of exsanguination point to selective maintenance of cerebral circulation at the expense of other areas of the body. Recent polarographic studies in dogs by Bloor et al.[2] likewise demonstrated compensatory maintenance of cerebral oxygenation during blood loss. As indicated previously, our results are at variance with those of Bloor et al. and demonstrate a linear drop in available cerebral oxygen during development of hypotension similar to that seen in most of the trimethaphan-treated animals. Moreover, comparison of the slopes of fall of cerebral oxygen (or cerebral blood flow) in four animals who underwent both types of hypotension indicated no significant difference. It was concluded that under the conditions of our experiments there was no evidence of advantage of exsanguination in preserving oxygen supply to the brain. On the other hand, there was no evidence that the cerebral circulation was protected more effectively by the use of trimethaphan. Because of the protection afforded experimental animals by autonomic blocking agents against irreversible shock, probably by preserving better perfusion of other vital organs, we favor the clinical use of chemical-induced hypotension when hypotension is indicated.

The duration of hypotension has been considered to be of fundamental importance in the use of hypotension clinically. Our studies indicate that there was no greater difficulty encountered in restoring cerebral blood flow after relatively prolonged hypotension than after shorter experiments. Furthermore, with hypotension lasting for

periods of 30 minutes there was no evidence of deterioration of the available cerebral oxygen. It is concluded, therefore, that as long as cerebral oxygenation is maintained at or above the normal range, there is no deleterious effect on the brain from prolonged lowering of blood pressure. Whether this is true with regard to other vital organs is not known, although Anlyan and associates,[1] noted a significant increase in mortality of dogs, due to liver damage, when experimental hypotension was prolonged from 30 to 45 minutes.

Emphasis has been placed in this report on the variability of the reaction to hypotension. This variation is noted in the configuration and slope of the decline of available cerebral oxygen, as well as in the level of pressure which is adequate to maintain normal cerebral oxygenation. Reports of other investigators are also impressive in this respect. The explanations for this variability probably include such factors as differences in relationship between cerebral and systemic arterial pressures, differences in compensatory vasodilatation, and differences in response of the cardiovascular systems to the blocking agent. It is therefore impossible to predict in any animal the margin of safety which exists in a given level of hypotension. The ideal arrangement, for clinical application, would be a continuously recording polarographic electrode to allow direct comparison of the available cerebral oxygen during hypotension with the known level of oxygenation during the normotensive state in that same subject.

Summary

Polarographic recording of available cerebral oxygen has been performed during hypotension induced by autonomic blockade and by exsanguination. In two-thirds of the experiments using chemical blockade there was recorded no compensatory maintenance of cerebral blood flow in the presence of hypotension. The same was true in all experiments using exsanguination. Absence of compensatory vasodilatation may be related to anesthesia. There was no evidence of preferential maintenance of cerebral circulation during exsanguination, and autonomic blockade seems preferable for clinical use. During 100%-oxygen breathing all animals were protected well below the usual clinical levels of induced hypotension, but there was marked variation in the level of blood pressure necessary for maintenance of normal oxygen supply to the brain. There was no evidence that prolonged hypotension above the safe level is harmful.

University of Cincinnati College of Medicine, Division of Neurosurgery.

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Abstracts from Current Literature

EDITED BY BERNARD J. ALPERS, M.D.

Diseases of the Spinal Cord

SARCOIDOSIS OF THE SPINAL CORD. A. MOLDOVER, A. M. A. Arch. Int. Med. 102:414 (Sept.) 1958.

A 24-year-old white man had a five-month history of radicular pain and flaccid weakness with areflexia of the lower extremities, accompanied by "cord bladder." Spinal fluid showed albuminocytologic dissociation. Miliary opacities demonstrated in the chest x-ray suggested the diagnosis of sarcoidosis, which was confirmed by inguinal-node biopsy. Hormone therapy, consisting first of corticotropin, followed by cortisone, resulted in prompt improvement in gait and bladder control. Relapse occurred each time the medication was discontinued for the first two years, after which the patient remained well for a one-and-one-half-year period without therapy. The favorable response of this patient to steroid therapy suggests its value in sarcoidosis of the central nervous system.

PARSONS, Montrose, N. Y.

MANEUVER TO HELP THE DIAGNOSIS OF RUPTURED DISK. B. C. SHERBOK, A. M. A. Arch. Surg. 76:986 (June) 1958.

In cases of ruptured disk, increased intraspinal pressure evoked by forceful expiration against closed mouth and nose may elicit or exaggerate the radicular pain.

LIST, Grand Rapids, Mich.

INFECTIONS OF VERTEBRAL INTERSPACES AFTER OPERATIONS ON INTERVERTEBRAL DISKS. C. R. SULLIVAN, W. H. BICKEL, and H. J. SVIEN, J. A. M. A. 166:1973 (April 19) 1958.

The bizarre symptoms associated with infection of the intervertebral space and the important biological after-effects of inflammation within this space prompted this detailed study of 11 patients with symptoms of infection after having undergone surgical removal of a nucleus pulposus. Diagnosis of this complication may be difficult because (*a*) failure of symptoms to appear immediately after operation, (*b*) usual absence of fever, and (*c*) the bizarre nature of the patient's complaints.

In four patients of this series the symptoms appeared within 4 or 5 days after operation; in two the symptoms were delayed as long as 10 weeks. The pain was sometimes excruciating and out of all proportion to the physical signs. Fever was not a prominent sign, and the only general laboratory test of significance in this connection was the sedimentation rate. The most important information was gained by aspiration of material from the involved interspace.

Progression of the inflammatory process within the interspaces to bony infusion appeared inevitable. The process became visible in roentgenograms in the course of a few weeks, and fusion occurred within six months to two years. Three representative case histories are given to illustrate the symptoms and signs encountered.

The most important treatment is adequate immobilization of the spinal column by means of plaster-of-paris cast or rigid brace. Appropriate antibiotics should be administered, and, in addition to the cast, rest in bed for a few weeks may also be necessary.

ALPERS, Philadelphia.

Peripheral and Cranial Nerves

NERVE INJURIES IN THE UPPER EXTREMITY. R. D. LARSEN and J. L. POSCH, A. M. A. Arch. Surg. 77:469 (Oct.) 1958.

Nerve injury is one of the major causes of disability in the upper extremities. Larsen and Posch have treated 325 such cases since 1950. It is of interest to note that 266 cases were not of industrial origin and that in 8 instances the nerve was injured by breaking a porcelain faucet. Accurate anatomic knowledge is a prerequisite to proper diagnosis and treatment. Whenever possible, a primary repair of the nerve(s) should be attempted, but in badly crushed or contaminated wounds or when no adequate operating facilities are available, secondary nerve repair is preferable. In general, return of sensory function is good, although it may remain incomplete in many instances. The degree of motor return varies greatly with different nerves;

the result of nerve suture is excellent with radial-nerve injuries above the elbow and satisfactory in at least one-half the median-nerve injuries at the level of the wrist. However, ulnar-nerve suture gives uniformly bad results, regardless of its location of the injury. If a nerve suture fails or is impossible, tendon-transfer operations may restore satisfactory function of the injured extremity.

LIST, Grand Rapids, Mich.

DIABETIC NEUROPATHY PRESENTING AS THE INITIAL CLINICAL MANIFESTATION OF DIABETES. M. ELLENBERG, Ann. Int. Med. 49:620 (Sept.) 1958.

Neuropathy occurring in association with diabetes mellitus need not always follow a prolonged period of poor diabetic control. Observations have been recorded of neuropathy actually preceding or accompanying the usual clinical manifestations of diabetes. The author presents four cases of the former.

The cases indicate the possibility of neuritis preceding the usual clinical manifestation of diabetes and actually being the presenting symptoms—not dependent on the presence of prolonged hyperglycemia or glycosuria.

The implications made by the author are as follows: 1. Such a diagnosis is to be suspected when the neurologic picture is compatible with or suggestive of the syndromes associated with diabetic neuropathy and/or occurring in a patient with a family history of diabetes. This should be followed up with a two-hour postprandial blood sugar test as a screening test and a glucose tolerance test as indicated. 2. The theoretical aspects indicate that carbohydrate disorders are but one aspect of diabetes mellitus and that it is actually a generalized complex, fundamental disease with many other facets, such as the complications of pregnancy, microangiopathy, comprising retinopathy and nephropathy, and arteriosclerotic involvement of the larger vessels.

AIGNER, Rochester, Minn.

MEDIAN NEURITIS (CARPAL TUNNEL SYNDROME) CAUSED BY GOUTY TOPHI. L. E. WARD, W. H. BICKEL and K. B. CORBIN, J. A. M. A. 167:844 (June 14) 1958.

Ward and his co-workers describe a case of bilateral compression of the median nerve at the wrist with resulting neuritis, unique in that compression was caused by the presence of large urate deposits in and about the carpal tunnels.

The patient was a 56-year-old man whose first attack of gout had occurred 15 years earlier. Two years before this admission he noted intermittent numbness and tingling of the first four fingers of each hand and pain in those fingers and in the wrists. The fingers, especially the thumbs, gradually weakened. He became almost incapacitated with respect to use of the hands.

Roentgenograms of the wrists and hands showed evidence of osteoporosis, and the concentration of uric acid was 10.2 mg. per 100 cc. of serum. Electromyography and measurement of conduction time showed the characteristic findings of prolonged conduction time from the wrist to the thenar muscles but minimal evidence of denervation in the muscles of the hand supplied by the median nerve, although this is usually demonstrable.

Treatment by surgical excision of the tophi and sectioning of the transverse carpal ligaments was successful. A diet low in purines and uricosuric agents was advised. Four months later there was marked improvement in strength and sensation in the hands.

The authors believe that surgical intervention affords quicker and more certain relief than might be expected from uricosuric agents and seems to be the treatment of choice in a case of this sort.

ALPERS, Philadelphia.

Treatment, Neurosurgery

AN AGENT EFFECTIVE AGAINST CRYPTOCOCCOSIS OF THE CENTRAL NERVOUS SYSTEM. A. BIDDLE and H. KOENIG, A. M. A. Arch. Int. Med. 102:801 (Nov.) 1958.

Two patients with cryptococcosis of the central nervous system were effectively treated with amphotericin B. In the first instance cycloheximide had been used without success, and the patient was moribund after a one-and-one-half-year course of infection, characterized by at least one remission, following surgical drainage of a frontal abscess. Improvement was noted after a few weeks of amphotericin therapy, and prompt clinical deterioration followed its temporary discontinuance during early administration of the drug. After approximately one year, amphotericin therapy was terminated, and seven months follow-up indicated no clinical or bacteriologic recurrence. Residuals of dementia and flaccid paraplegia were, however, reported. The second patient developed cerebral cryptococcosis following a course of x-ray

therapy for Hodgkin's disease. A month's course of amphotericin therapy was terminated as a result of the development of viral hepatitis, but no recurrence of the fungous infection had taken place during a subsequent seven months' follow-up period, at which time the patient was described as asymptomatic and back at work.

PARSONS, Montrose, N. Y.

TREATMENT OF TETANUS. G. KOURANY, E. A. CLEVE, and F. P. SMITH, A. M. A. Arch. Int. Med. 102:823 (Nov.) 1958.

The authors review a group of 70 patients treated for tetanus at the Gorgas Hospital from 1905 to 1956. Treatment is analyzed from the standpoint of the local wound, the circulating toxin, and the effect of fixed toxin. Treatment of the local wound is nonspecific for tetanus; but the use of antitoxin for the neutralization of circulating toxin in the second phase, and sedation and tracheotomy for the central nervous system effects of fixed toxin during the third phase, has been instrumental in reducing the tetanus death rate from over 80% to less than 20%. The clinical experiences are supplemented by experimental data from the literature, showing that neutralization of circulating toxin by antitoxin and prevention of asphyxia and convulsions enabled animals to survive after having received many times the usual lethal dose of tetanus toxin.

PARSONS, Montrose, N. Y.

HYPOPHYSECTOMY IN MAN. O. H. PEARSON, B. S. RAY, M. B. LIPSETT, H. HOOD, and E. GREENBERG, A. M. A. Arch. Surg. 77:144 (July) 1958.

The authors report their experiences with hypophysectomy by means of a picture exhibit. The indications for hypophysectomy are (1) metastatic cancer of the breast, (2) acromegaly which has not responded to radiation, (3) other pituitary tumors, (4) diabetes mellitus with vascular complications, and (5) possibly, metastatic cancer from the prostate.

The rationale of hypophysectomy in breast cancer is the suppression of estrogen secretion of ovaries and adrenals (and accessory ovarial and adrenal tissues) and elimination of pituitary growth hormone and prolactin. In 55% of the cases of metastatic breast cancer objective improvement was obtained by hypophysectomy (visible regression of lesions). The mean duration of remission after operation was more than 10 months, with a range of 2-30 months and a mean survival time of more than 13 months in the improved cases. Hypophysectomy is about equally effective in premenopausal and postmenopausal patients. It achieves remission even after castration and/or adrenalectomy. The cancer-stimulating effect of estrogen and growth hormones could be shown by the increased urinary calcium excretion. As a result of hypophysectomy, an adrenal crisis may develop unless adequate substitution therapy with cortisone is given. Since the hypothalamic-pituitary connections are damaged by hypophysectomy, diabetes insipidus develops, but this complication is less severe if the hypophyseal stalk is severed as low as possible.

The surgical technique and endocrine management are described in detail. Postoperative maintenance therapy is essentially with cortisone 37.5-50 mg., daily, thyroid 120-180 mg., daily, and vasopitressin tannate 2-5 units.

LIST, Grand Rapids, Mich.

TREATMENT OF CRYPTOCOCCAL MENINGITIS WITH AMPHOTERICIN B: A NEW FUNGICIDAL AGENT. M. J. FITZPATRICK, H. RUBIN, and C. M. POSER, Ann. Int. Med. 49:249 (Aug.) 1958.

The authors report three cases of Cryptococcus meningitis treated with amphotericin B. The first case was that of a 56-year-old man with silicosis, nodular lesions of the lungs with a negative tuberculin skin test, bilateral renal calcinosis, and azotemia. Numerous cryptococci were found in his bronchial secretions and also in his urine. He developed rapid progressive meningitis and died despite treatment with amphotericin B.

The second case was that of a 31-year-old housewife who had had chronic Torula meningitis for seven months before treatment was started. Although the fungus was found in the cerebrospinal fluid, no portal of entry or extracerebral focus was evident. The treatment was to give the amphotericin B intravenously—50 mg. in 1,000 cc. of 5% dextrose in water—for two weeks. This amount was later increased to 100 mg., given the same way. After one month of therapy her symptoms cleared, and after three months the cerebrospinal fluid was normal. There was no recurrence evident after nine months.

The third case that of a 45-year-old Negro who had had chronic central nervous system infection with Cryptococcus neoformans for at least eight years. Treatment with amphotericin B cleared the cerebrospinal fluid of fungi but did not alter the residual neurologic picture.

The administration of the drug may be accompanied by side-reactions, including chills with fever, which can be minimized by giving acetylsalicylic acid or antihistamines as premedication. Transient increase of urea nitrogen has been noted with higher doses of the drug, but no changes in the hematopoietic, hepatic, renal, cutaneous, or nervous systems have been observed. The optimal dosage and duration of treatment have not been determined, but since blood levels following intravenous treatment persist for up to 18 hours, infusions of the drug in higher doses are being used on alternate days.

AIGNER, Rochester, Minn.

COMPLICATIONS IN POSTERIOR FOSSA DUE TO OCCIPITAL TRAUMA—THEIR OPERABILITY. R. G. FISHER, J. K. KIM, and E. SACHS, J. A. M. A. 167:176 (May 10) 1958.

Fisher and his co-workers stress the importance of recognition and operability for hemorrhage and fluid accumulations in the posterior fossa as a result of cranial injury, in their survey of 300 cases in which trauma to the occipital region of the head was the cause of the patient's seeking medical attention.

Roentgenographic examinations were made on all but four patients. Of the 296 patients, 98 were found to have fractures, varying in their appearance, in the occipital bone. Of the 98 patients having a fracture of the occipital bone, 32 presented serious complications; and of the 198 not having a fracture, only 14 presented serious complications.

The 21 cases here described by the authors involved lesions in the posterior fossa and included 2 fatal cases of intracerebellar hemorrhage. There were eight cases of extradural hemorrhage in this region; decompression or removal of clots was followed by complete recovery in seven of these cases. The eighth patient was not relieved by making a burr hole in the occipital region: He died after a lumbar puncture, and autopsy revealed both an extradural hemorrhage and bilateral subdural hematoma. Subdural hematoma was found in four patients, three of whom died. It is believed that all patients might have been saved had burr holes been placed in both the supratentorial and the infratentorial region.

Subdural hygroma occurred in seven patients, and all survived; more rapid improvement resulted from the making of burr holes into the posterior fossa, to permit the escape of trapped cerebrospinal fluid and to reduce the intracranial pressure.

In the past, attention has been focused on lesions to the surface of the cerebral hemispheres. These cases show that similar attention should be given to the structures in the posterior fossa. Fisher et al. point out that patients with injury to the occiput who have a fracture or evidence of local hematoma with progressive embarrassment of vital signs, prolonged coma, or progressive cerebellar signs should undergo surgical exploration. This is carried out by placing burr holes both above and below the tentorium.

ALPERS, Philadelphia.

TRIETHYLENETHIOPHOSPHORAMIDE IN THE TREATMENT OF METASTATIC CEREBRAL MALIGNANCY. P. L. DAVIS, M. H. SHUMWAY, and B. SIU, J. A. M. A. 167:726 (June 7) 1958.

Davis and associates describe a case of chronic, secondary diabetes insipidus occurring in a 68-year-old woman. It was due to metastatic cancer to the pituitary stalk, the primary lesion being in the tail of the pancreas. The condition was occult but was suspected of being malignant, and was treated as such because of a lack of therapeutic response with the usual treatment.

Three injections, in all, of triethylenethiophosphoramide (Thio-TEPA) were given. The first dose, of 40 mg., was injected into the right common carotid artery in the same manner as that used in angiography. A remission of almost six months resulted. Symptoms gradually reappeared, and the same dose was given in the left common carotid artery. This time the favorable response lasted three to four months. The third dose was 50 mg., injected in the right carotid artery, but the remission lasted only 28 days. The patient was then given 3,600 r (in air), with use of a 250-kv. machine and a 5-cm. cone. A partial remission of three weeks followed, but she became progressively weaker and died. Postmortem examination revealed a carcinoma, 1 cm. in diameter, in the tail of the pancreas and a metastasis, measuring 4 mm., in the pituitary stalk in the region of the hypothalamic supraoptic nuclei.

ALPERS, Philadelphia.

THROMBOLYSIS WITH FIBRINOLYSIN IN CEREBRAL ARTERIAL OCCLUSION. B. J. SUSSMAN and T. S. P. FITCH, J. A. M. A. 167:1705 (Aug. 2) 1958.

Sussman and Fitch treated three patients with hemiplegia by the slow intravenous infusion of fibrinolysin. The site of occlusion of the cerebral vessels was located in each case by arteriography. In one case partial clearing of occluded carotid lumen was observed. The second

patient showed no alteration of his anterior cerebral artery occlusion. In the third, the angiograms clearly showed nonfilling of the middle cerebral group of arteries before treatment, while on the eighth day after beginning treatment good filling of the middle cerebral vessels was obtained. This patient showed the most favorable results. The history of rheumatic heart disease and the fact that treatment was commenced within six hours after the onset of symptoms suggest that the lesion was caused by an embolus originating in the fibrillating left atrium, and that the embolus was a fresh thrombus, most susceptible to the lytic agent.

The authors are impressed with the possible advantageous action of fibrinolysin. They believe that its prompt administration in cases of cerebral thrombosis or embolism may prove beneficial. It is not expected to benefit patients with progressive atherosclerotic occlusion in whom an actual thrombus does not occlude the lumen.

No detrimental effects that could be ascribed either to the diagnostic angiography or to the administration of fibrinolysin were observed in these patients.

ALPERS, Philadelphia.

INTRAVENOUS PHENYTOIN SODIUM IN CONTINUOUS CONVULSIONS IN CHILDREN. P. K. A. McWILLIAM, Lancet 2:1147 (Nov. 29) 1958.

McWilliam reports that in 10 of 11 children continuous or recurrent convulsions, which had shown no signs of terminating spontaneously, ceased after intravenous diphenylhydantoin (phenytoin) sodium was given. In six patients the convulsions ended within 10 minutes of the start of one slow intravenous injection of diphenylhydantoin, the doses being 175, 50, 150, 200, 200, and 25 mg., respectively. The injections were prepared by adding 5 cc. of diluent to 250 mg. (grains 3¾) of powdered diphenylhydantoin sodium in a rubber-capped vial, and shaking until solution is complete. The diphenylhydantoin dissolved slowly, and from 5 to 10 minutes of shaking is required, although the process may be accelerated by warming. The solution should be clear, and is best used within two to three hours of preparation. It should not be used if there is any discoloration. The effective dosage employed by this author ranged from 25 to 500 mg., and the injection was usually effective within ten minutes.

YASKIN, Camden, N. J.

ACETAZOLAMIDE THERAPY IN EPILEPSY. I. P. ROSS, Lancet 2:1308 (Dec. 20) 1958.

Ross reports his results in 63 epileptic patients treated with acetazolamide (Diamox). It appeared to be helpful in 2 of 17 children with petit mal. Acetazolamide had no effect in 46 adults (24 with petit mal and grand mal, 12 with temporal lobe attacks, and 10 with miscellaneous forms of epilepsy), or on epilepsy related to menstruation. From the results of his experience he concluded that acetazolamide was of no value in the management of chronic epilepsy in adults and was seldom of value in children with petit mal. Acetazolamide was given in doses of 750 mg. daily, sometimes starting with a small dose of 250 mg. and later increasing. Children under 12 received 125 mg., increasing to 500 to 750 mg. daily. This trial of therapy in these cases lasted from two to six months.

YASKIN, Camden, N. J.

Muscular System

MYXEDEMA, PSEUDOMYOTONIA, AND MYOTONIA CONGENITA. L. W. JARCHO and F. H. TYLER, WITH THE TECHNICAL ASSISTANCE OF K. E. JOHNSON, A. M. A. Arch. Int. Med. 102:357 (Sept.) 1958.

A 39-year-old white woman with a positive family history of myotonia developed myxedema with myotonia following subtotal thyroidectomy. The syndrome was characterized by delayed muscular relaxation with prolonged contraction on direct muscle percussion with characteristic "dive bomber" decrescendo variety of myotonic electromyographic change and hyperkeratosis of palms and soles. Specific hormone therapy produced a favorable response. In contrast, eight additional hypothyroid patients studied presented pseudomyotonia, consisting merely of delayed muscular relaxation without prolonged contraction on direct muscular percussion, and no "warming-up" effects or electrical changes. Differential diagnosis includes myotonia congenita, paramyotonia, and myotonic dystrophy. Muscular disorders encountered in hypothyroidism include pseudomyotonia, occasionally myotonic dystrophy, the Hoffmann syndrome of hypertrophied and stiff muscles with delayed relaxation, the hypertrophied hard muscles of myxedemic children (Debré-Sémelaigne syndrome) and rarely, Thomsen myotonia congenita, the existence of which may become evident only after thyroid insufficiency, as occurred in the current instance. In the latter situation a positive family history will almost inevitably be present.

PARSONS, Montrose, N. Y.

MUSCULAR DYSTROPHY IN SARCOIDOSIS. B. MCCONKEY, A. M. A. Arch. Int. Med. 102:443 (Sept.) 1958.

A 39-year-old woman presented a problem of muscle weakness characterized by remissions and exacerbations over a 12-year period. Muscle biopsy revealed sporadic degeneration of muscle fibers with small noncaseous granulomatous foci, consisting of endothelial, giant cells, and lymphocytes. Chest films were normal, as were all tests for tuberculosis, but the Mantoux test was negative, and γ-globulin value was increased. Cerebrospinal fluid protein was elevated. Remission followed isoniazid, streptomycin, and cortisone. Death from an apparent heart attack occurred, and permission for autopsy was not obtained. The literature concerning muscle lesions in sarcoidosis was reviewed. There have been 53 cases, one-half of which have presented clinical evidence of muscle disease, usually in the form of nodules on examination; only half have complained of muscle weakness, which in two-thirds presented a characteristic picture of dystrophy. Opinion is divided as to the value of steroid therapy.

PARSONS, Montrose, N. Y.

Encephalography, Ventriculography and Roentenography

THE LATERAL ROENTGENOGRAM OF THE NECK. M. H. WHOLEY, A. J. BRUWER, and H. L. BAKER, Radiology 71:350 (Sept.) 1958.

Wholey, Bruwer, and Baker reviewed 700 lateral roentgenograms of the cervical spine drawn from the files of the Mayo Clinic. About 600 of these roentgenograms were considered technically adequate and without abnormality. Since the roentgenograms had been made at a 60-in. target-to-film distance, the factor of distortion was ignored, and measurements were made directly on the film. The retropharyngeal space, measured between the inferior-anterior border of the second cervical vertebra and the pharyngeal airway, had a normal range of from 1 to 7 mm. in the adult. The retrotracheal space, measured from the inferior-anterior margin of the sixth cervical vertebra to the posterior surface of the tracheal air column, had a normal range of 9 to 22 mm. in the adult. The cervical spinal canal showed various ranges of normal in the sagittal diameter, depending upon which vertebral level was measured.

The middle half of the upper end of the odontoid process normally lies directly beneath the basion, and an average of 5 mm. from it, in the adult. The anterior surface of the odontoid process is normally within 1 or 2 mm. of the posterior surface of the anterior arch of the atlas. These relationships are relatively constant and of great importance. Small variations in these relationships are usually associated with clinical symptoms. They are much more important in evaluating the status of the upper portion of the cervical spinal canal than is Chamberlain's or McGregor's line. Variations in the relationship of the odontoid process to either Chamberlain's or McGregor's line are usually without significance if the normal odontoid-atlas-basion relationship is maintained.

WEILAND, Grove City, Pa.

CONGENITAL FUSION OF THREE LUMBAR VERTEBRAL BODIES. S. STANISAVLJEVIC and E. G. ST. JOHN, Radiology 71:425 (Sept.) 1958.

Congenital fushion of cervical vertebral bodies is fairly common. In the thoracic spine such fusion occurs less frequently, while it is rare in the lumbar portion of the spine. Stanisavljevic and St. John report the case of a woman, aged 44, who was found to have congenital fusion of the first, second, and third lumbar vertebral bodies, associated with hypoplasia of the eighth thoracic vertebra and a congenital fusion of the right eighth and ninth ribs.

WEILAND, Grove City, Pa.

CHOLESTEATOMA OF THE TEMPORAL BONE. H. CHIAT and R. D. KITTREDGE, Radiology 71:559 (Oct.) 1958.

Chiat and Kittredge have reviewed all of the endaural mastoidectomies performed at their hospital during the last 10 years. There were 74 of these operations. In 2 of the patients operation revealed carcinoma, and in the remaining 72 chronic suppurative otitis media with perforation. Twenty-eight cholesteatomas were found. Of these 28 cases, 25 had had adequate roentgenograms before operation, and it was possible in retrospect to make a roentgen diagnosis of cholesteatoma in 13 of these cases.

Mayer's view has been popular for roentgenographic demonstration of cholesteatomata, but Chiat and Kittredge believe that the fronto-occipital (Chamberlaine-Towne) position is the position that oftenest clearly defines a cholesteatoma. The most important diagnostic feature is enlargement of the mastoid antrum. Since cholesteatoma usually is associated with a good

bit of sclerosis of the surrounding bone, tomographic studies of the mastoid process in the fronto-occipital projection are very helpful in making the preoperative diagnosis of cholesteatoma. Chiat and Kittredge consider the upper limits of normal for the mastoid antrum to be 12 mm. in height and 6 mm. in width. Enlargement of the antrum with a sharp outline favors cholesteatoma, while an indistinct outline favors an inflammatory osteitis.

WEILAND, Grove City, Pa.

IMPORTANCE OF THE AIR SHADOW OF THE CISTERNA MAGNA IN ENCEPHALOGRAPHIC DIAGNOSIS. C. M. GREENWALD, M. EUGENIO, C. R. HUGHES, and W. J. GARDNER, Radiology 71:695 (Nov.) 1958.

Gardner and his associates perform pneumoencephalography as a surgical procedure on the operating floor, with all necessary surgical and anesthetic facilities at hand. Pneumoencephalography is performed on patients with increased intracranial pressure, but in these cases instruments are laid out and the scalp is prepared for craniotomy before the pneumoencephalography is performed. Pneumoencephalography is not performed when obstructive hydrocephalus is suspected, except in a few instances in which it is preceded by a ventricular tap to relieve the intracranial tension. Over a period of 28 years' experience pneumoencephalography has proved to be a safe procedure if these precautions are observed. Gardner and his associates feel that the use of ventriculography in place of encephalography in cases of suspected cerebral tumor without increased intracranial pressure is not to the patient's best interests, because pneumoencephalography discloses surgical lesions which cannot be demonstrated in any other manner than by exploratory craniotomy.

Gardner and his associates perform pneumoencephalography with the patient under anesthesia. Spinal fluid and air are replaced alternately in 5 cc. amounts, taking pressure readings at frequent intervals. This process is continued until air is recovered from the needle in the lumbar portion of the spinal canal. Thus, one usually gets good filling of the basal cisterns and an air myelogram of the cervical region, in addition to the demonstration of the ventricular system of the brain.

During the year 1956 Gardner and his associates obtained pneumoencephalograms on 306 patients, ventriculograms on 35 patients, and cerebral arteriograms on 245 patients. Fifty-two patients had both a preoperative pneumoencephalogram and a craniotomy. In 31 cases lesions were located supratentorially. In all these there was no demonstrable defect in the gas shadow of the cisterna magna. In 15 of the cases the roentgen study led to a surgical exposure of the posterior fossa. In 10 of these 15 cases the shadow of the cisterna magna was abnormal. Of the 15 patients, 7 proved to have expanding lesions (tumors or hematomas). One showed no surgical lesion. In the remaining seven patients, lesions, such as the Dandy-Walker syndrome, the Arnold-Chiari malformation, basilar impression, or syringomyelia, were found.

WEILAND, Grove City, Pa.

TUBEROUS SCLEROSIS: REPORT OF A CASE WITH EPENDYMOMA. W. C. MACCARTY JR. and D. G. RUSSELL, Radiology 71:833 (Dec.) 1958.

Tuberous sclerosis is a relatively rare familial disease. The basic disorder is a defect in development of ectodermal structures, usually with a widespread distribution involving many systems. The classical clinical triad consists of mental deficiency, epilepsy, and sebaceous adenomas of the face. Pale, firm, "potato-like" nodules, ranging in size up to 3 cm. in diameter, are found scattered throughout the cortex of the brain. Subependymal tumor masses frequently occur in the lateral ventricles. Congenital tumors of the retina, called phakomas, are also seen. Other skin lesions aside from the typical sebaceous adenomas of the face have been found in this disease. Visceral lesions, consisting of mixed embryonal elements, have been reported in almost every organ.

Intracranial calcification has been demonstrated in about 60% of cases of tuberous sclerosis seen by some authors. Rounded patches of sclerotic bone involving the inner table of the calvaria also are a frequent finding. Ventriculograms will demonstrate the subependymal tumors. Radiographs of the hands and feet show characteristic cysts in the phalanges and periosteal new-bone formation in the metatarsals.

MacCarty and Russell describe the case of a patient with tuberous sclerosis who developed right-sided headaches, diplopia, and blurred vision. The patient ultimately came to surgery and died after operation. She was found to have a tumor in the right lateral ventricle, part of which histologically appeared to be the usual nonmalignant subependymal mass, which is seen in tuberous sclerosis, but part of which consisted of ependymal cells arranged in a rosette

pattern around blood vessels. Because of this latter finding, an ependymoma was thought also to be present in the ventricle. Members of the patient's family later were studied, and two additional cases of tuberous sclerosis were discovered.

WEILAND, Grove City, Pa.

RADIOLOGIC ASPECTS OF CRANIOPHARYNGIOMAS. D. J. BARNETT, Radiology 72:14 (Jan.) 1959.

Between the years 1932 and 1956 the diagnosis of craniopharyngioma was made in 84 patients at the Neurological Institute of New York. In only 62 of these 84 cases were adequate clinical records and roentgenographic data available. This report deals with an analysis of these 62 cases. A tissue diagnosis was made in 48 of them. The other 16 cases were diagnosed clinically and roentgenologically. Craniopharyngiomas develop from cell rests of the craniopharyngeal duct, a structure which is formed during the embryonic state by contraction of Rathke's pouch. Shanks and Kerley carefully sectioned the contents of the sella turcica in a number of patients and found remnants of Rathke's pouch in 20% of the patients examined. However, craniopharyngiomas are relatively rare.

Craniopharyngiomas develop just above the pituitary fossa in most cases. The first symptoms usually are visual disturbances, caused by pressure on the optic chiasm. Endocrine disturbances appear as the tumors encroach upon the pituitary gland. When the tumor becomes large enough, it can compress the third ventricle sufficiently to produce obstruction and dilatation of the lateral ventricles. This is followed by signs of increased intracranial pressure.

The sella turcica usually was not enlarged when a craniopharyngioma was present. In a few patients, however, it was very large. In about half the patients the anterior clinoid processes appeared normal. When the anterior clinoid processes were abnormal, the usual involvement was erosion of their inferior surfaces, causing the processes to appear pointed. The dorsal surfaces rarely showed any abnormal change. The dorsum sellae and the posterior clinoid processes frequently showed erosion. In only 12 patients was the dorsum sellae considered normal. An increase in density of bone around the sella turcica was an unexpected abnormal finding in seven patients. Sometimes this increased density was limited to the clinoid processes, sometimes to the floor, and sometimes both regions were involved.

Abnormal calcification was found in and about the sella turcica in 43 patients (69% of the cases). Other observers have reported visible calcification in 55% to 80% of roentgenograms of the skulls of patients with craniopharyngiomas.

Of the 62 patients, 40 were examined by pneumoencephalography or ventriculography. Only 2 of these 40 did not show compression of the third ventricle. Ninety-five per cent of those examined had some distortion of the third ventricle. The lateral ventricles were enlarged in 27 patients. Carotid angiography was performed on only a few of the patients. Little displacement of the internal carotid artery is found, for the tumors expand predominantly upward. The tumor can displace the artery upward and produce an appearance of widening of the carotid siphon and an elevation of the origin of the anterior cerebral arteries.

Other brain tumors can simulate craniopharyngioma. Cystic astrocytomas, chromophilic pituitary adenomas, chordomas, and oligodendrogliomas have been found in the region of the sella turcica and have produced calcific deposits in the roentgenogram which were identical with those found in craniopharyngioma.

WEILAND, Grove City, Pa.

CAROTID ANGIOGRAPHY IN THE LOCALISATION OF SUPRATENTORIAL NEOPLASMS AND HAMARTOMATA. P. F. J. NEW, Radiology 72:35 (Jan.) 1959.

New's material consists of 131 patients who had supratentorial neoplasms and arteriovenous malformations and who were studied and the nature of the abnormality verified between 1952 and 1957. These 131 cases were derived from a large series of 213 intracranial neoplasms and hamartomata which were fully investigated during that period of time. All but one of the patients had cerebral angiography performed. Twenty-one of them had encephalography, and 14 of them had ventriculography. The abnormality finally found in 48% of the 213 cases was a glioma. Meningioma was found in 8%; cerebral metastases were found in 6%, and arteriovenous malformations in 10%. The remaining 28% of cases were of conditions other than supratentorial neoplasms and arteriovenous malformations.

New believes that cerebral angiography can be safer and less disturbing to the patient than pneumography. The technical procedure consumes less time. In a total of 757 angiographies performed at the University of Western Ontario there were no deaths attributable to the

procedure, and very few complications of any importance. New believes that the majority of supratentorial space-occupying lesions are best examined first by carotid angiography. A pathological diagnosis and a satisfactory localization of the lesion will frequently be provided by this method of study alone. Avascular space-occupying lesions of the occipital or parietal lobes, avascular midline basal tumors, and very small or very early lesions may not be accurately localized or even detected. A moderate number of patients will require additional pneumography after cerebral angiography. Usually encephalography will then prove to be the procedure of choice. Pneumography should be the first study performed when an avascular midline basal tumor (pituitary adenoma, craniopharyngioma, etc.) is suspected. Despite the high degree of accuracy of cerebral angiography, it must be borne in mind that occasionally a large and very extensive infiltrating glioma can exist with no definite angiographic or pneumographic abnormality. Thorough clinical examination and a high index of suspicion remain the main safeguards against such tumors.

WEILAND, Grove City, Pa.

CONGENITAL INSENSITIVITY TO PAIN: A NEUROLOGIC SYNDROME WITH BIZARRE SKELETAL LESIONS. F. N. SILVERMAN and J. J. GILDEN, Radiology 72:176 (Feb.) 1959.

Silverman and Gilden report the case histories of two sisters who were seen because of bizarre skeletal malformations of unknown cause. Previous diagnoses of rickets, exostoses, and congenital deformities had been made at other institutions. The girls were studied over a period of time, and various orthopedic corrections were made. During most of the time of study of the older girl, the orthopedic consultants favored a diagnosis of the Ehlers-Danlos syndrome. A dermatological consultant did not concur with this diagnosis. It was not until there had been a fairly long period of observation of both girls that the observation was made, and generally accepted by the physicians treating them, that the girls were relatively insensitive to pain. During the period of observation the older sister suffered a fracture of the distal epiphysis of the tibia at the ankle joint, with displacement of the epiphysis and considerable swelling and discoloration. The fracture was not diagnosed radiographically until 12 days after the injury, during which time the patient had been walking on the ankle. Pain was not a complaint at the time of fracture, during the time the patient walked on the fracture, or at the time of examination.

During the period of observation the younger sister fell on an icy street and broke the shaft of her left femur. She felt the bone snap and was aware of immediate numbness of the entire lower extremity after the fracture. However, she complained of no pain at the time of fracture or during the subsequent treatment. Finally, a neurologist was asked to examine the younger sister. Sensations of touch, vibration, and position were intact. The pain produced by pinprick was very slight. Corneal reflexes were almost absent. It was thought that the corneal reflex which was present was visual, for the child could easily refrain from blinking when the eye was touched by cotton if she was instructed to do so. Neurologic reexamination seven years later showed no neurologic deficit other than a diminished sensitivity to pain. The older girl could not be studied neurologically because she refused examination and would not participate in any further study.

The syndrome of congenital insensitivity to pain is seen in infants in the form of severe biting of the tongue and lips as soon as the first teeth appear. Fingers may be bitten and multilated. The teeth are often lost early, owing to dental sepsis. Severe cuts, burns, and brusies are frequent and may heal poorly as a result of infection and improper care. Corneal opacities may result from trauma or foreign bodies in the eye. Fractures and dislocations may occur, which are not diagnosed or treated because of the absence of pain. They may later be misdiagnosed as congenital abnormalities or some obscure form of dysplasia of the bones because a history of fracture or trauma is difficult to elicit. The patient is not likely to give the history of diminished sensitivity to pain because he may be totally unaware that his low sensitivity to pain is abnormal. Members of the family, also, may not mention the patient's low sensitivity to pain in the history, even though they may be aware of it and might very well describe it in different words if questioned about it. Anatomical abnormalities of the nerve endings, nerve trunks, or central nervous system are usually absent. Complete gross and histologic examination of the entire nervous system of such a person has not yet been reported, but the brain and upper cervical spinal cord have been studied. Syphilis of the central nervous system and syringomyelia have been excluded clinically in the cases which have been reported. The clinical course is usually incompatible with hysterical analgesia.

Silverman and Gilden conclude that "the condition of congenital insensitivity to pain is a poorly understood, probably hereditary condition of variable expressivity which can be suspected on the basis of roentgen studies when skeletal lesions are present. Careful clinical questioning and examinations are required to confirm the diagnosis."

WEILAND, Grove City, Pa.

News and Comment

ANNOUNCEMENTS

Neuroanatomy Training Program.—A postgraduate training program in neuroanatomy has been established at Columbia University College of Physicians and Surgeons. This program, operated in conjunction with similar programs in other basic neurological sciences and the Neurological Institute, is designed to provide an appropriate foundation for an investigative or academic career. Opportunities will be available for preliminary course work in all of the basic neurological sciences and related fields. Training offered under this program includes (1) histochemistry of neural tissue, (2) degeneration and regeneration of neural tissue, (3) developmental and comparative neurology, (4) experimental neurology, (5) stereotaxic methods and their application, (6) histogenesis of neural tissue, (7) tissue culture studies of neural tissue, and (8) electron microscopic structure of sensory receptors, neural tissue, and muscle.

Candidates holding the M.D. or the Ph.D. degree will be eligible for consideration. Fellowships will be awarded for a period of, at least, one year, and will be renewable. Stipends will be arranged in accordance with need and qualifications. For additional information, write Malcolm B. Carpenter, M.D., Department of Anatomy, Columbia University College of Physicians and Surgeons, 630 W. 168th St., New York 32.

Positions in Infant Neurology.—Training in developmental pediatrics and infant neurology is available for Board-eligible physicians at the Clinic of Child Development of the Children's Hospital, Columbus, Ohio, on two levels. The first is a fellowship for physicians, preferably pediatricians, recently completing their residencies, with an opportunity to continue at faculty status in the teaching and research program. American citizenship is required. For those with additional qualifications, whether in pediatrics or in other fields, there is available a full-time staff appointment in the Department of Pediatrics of the Ohio State University College of Medicine, with major responsibility in teaching and research. For further information, please write to the Clinic of Child Development, Children's Hospital, 561 S. 17th St., Columbus 5, Ohio.

Kenny Foundation Scholarship Foundation.—The Sister Elizabeth Kenny Foundation announces continuation of its program of postdoctoral scholarships to promote work in the field of neuromuscular diseases. These scholarships are designed for scientists at or near the end of their fellowship training in either basic or clinical fields concerned with the broad problem of the neuromuscular diseases.

The Kenny Foundation Scholars will be appointed annually. Each grant will provide a stipend for a five-year period at the rate of $5,000 to $7,000 a year, depending upon the scholar's qualifications. Candidates from medical schools in the United States and Canada are eligible.

Inquiries regarding details of the program should be addressed to Dr. E. J. Huenekens, Medical Director, Sister Elizabeth Kenny Foundation, Inc., 2400 Foshay Tower, Minneapolis.

American Neurological Association.—The American Neurological Association elected the following officers:

President	Derek Denny-Brown, Boston
President-elect	Harold G. Wolff, New York
First vice-president	Charles Rupp, Philadelphia
Second vice-president	Samuel Brock, New York
Secretary-treasurer	Melvin D. Yahr, New York
Assistant secretary	Clark H. Millikan, Rochester, Minn.

Councillors

Percival Bailey, Chicago
Johannes M. Nielsen, Los Angeles
H. Houston Merritt, New York
Israel Wechsler, New York
Bernard J. Alpers, Philadelphia
Alexander T. Ross, Indianapolis
Benjamin Boshes, Chicago

Federal Neuropathology Training Grant Awarded to University of Maryland School of Medicine.—A postgraduate training program in neuropathology has recently been established in the Division of Neuropathology at the University of Maryland School of Medicine, in Baltimore. Aided by a grant from the National Institute of Neurological Diseases and Blindness, the program is designed particularly for Board-certified pathologists or those eligible for certification who plan an academic career and who desire specialty training in neuropathology. In addition to the neuropathologic training, a two-year progressive program includes instruction in the basic sciences as applied to neuropathology and some clinical correlative experience. Inquiries should be addressed to John A. Wagner, M.D., University of Maryland School of Medicine, Baltimore 1.

Training Fellowship Offered at New York University-Bellevue Medical Center.—New York University-Bellevue Medical Center is offering a three-month training fellowship with stipend in neuroanatomy and neurophysiology, beginning September, 1959. For information, apply to Dr. Louis Hausman, Department of Anatomy, New York University-Bellevue Medical Center, 550 First Ave., New York 16.

SOCIETY NEWS

Association for Research in Nervous and Mental Disease, Inc.—The annual meeting of the Association for Research in Nervous and Mental Disease will be held on Dec. 11 and 12, at the Hotel Roosevelt, New York. The subject of the meeting will be "Mental Retardation."

Sociedade Brasileira de Neurocirurgia.—The Brazilian Society of Neurosurgery will hold its Second Annual Congress this year, at the Grande Hotel de Campos do Jordão, from Sept. 10 to 13. The official subject will be Spinal Medullary Surgery; Sciatic Surgery.

PERSONAL

Dr. Francis C. Grant Delivers Annual Charles A. Elsberg Lecture.—Dr. Francis C. Grant, Emeritus Professor of Neurological Surgery, University of Pennsylvania School of Medicine, University Hospital, Philadelphia, delivered the Annual Charles A. Elsberg Lecture on Tuesday, May 19, 1959, at 8:30 p. m. at the New York Academy of Medicine, 2 E. 103d St., New York, on the topic "Trigeminal Neuralgia."

American Board of Psychiatry and Neurology, Inc.—In February, 1959, the American Board of Psychiatry and Neurology, Inc., was authorized to undertake subspecialty certification in Child Psychiatry. The following physicians, all certified specialists in General Psychiatry of the American Board of Psychiatry and Neurology, Inc., have been certified in the subspecialty of Child Psychiatry:

Frederick H. Allen, M.D. ..... Philadelphia
Frank J. Curran, M.D. ..... New York
Othilda Krug, M.D. ..... Cincinnati
William Siddon Langford, M.D. ..... New York
Hyman S. Lippman, M.D. ..... St. Paul
Joseph Franklin Robinson, M.D. ..... Wilkes-Barre, Pa.

The names of these new certified specialists in Child Psychiatry will appear as certified in Psychiatry (P) in the Directory, and the additional symbol of (ChiP) will indicate their certification in Child Psychiatry.

Books

The Central Nervous System and Behavior. Mary A. B. Brazier, Editor. Price, $5.25. Pp. 450. The Josiah Macy, Jr. Foundation, 16 W. 46th St., New York, 1959.

Brain-Memory-Learning. By W. Ritchie Russell. Price, $4.50. Pp. 140. Oxford University Press, 114 Fifth Ave., New York, 1959.

The first of these volumes presents the transactions of the first Conference on the Central Nervous System and Behavior, sponsored by the Josiah Macy, Jr. Foundation and the National Science Foundation, held in Princeton, N. J., in February, 1958. The twenty-eight participants represented a wide spectrum of scientific disciplines—neurophysiology, neuroanatomy, psychology, pharmacology, neurosurgery, neuropathology, psychiatry, and neurology.

The subject matter of the conference may conveniently be divided into two spheres, the first being an exposition of Russian scientific history and achievements, particularly with respect to neurophysiology, from its foundation, under Peter the Great, to the present. The book begins with a long pictorial review of Russian contributions to the understanding of the nervous system, comprising 107 full pages presenting portraits of most important historical Russian scientific figures, often pictured at their work, sometimes along with illustrations from their publications. This is followed by a series of brief discourses sketching the history of Russian neurophysiological thought and accomplishments. Of particular interest are Dr. Brazier's discussion of the work and theory of Sechenov (who perhaps fathered the concept of conditioned reflexes by his theory that all behavior is a balance between inhibition and excitation operating mechanically at the central link of the reflex arc, whose afferent flow might be a memory trace), Dr. Gantt's evaluation of the work of Pavlov, and Dr. Yakovlev's presentation of the contributions of Bechterew. The work of Danilevsky, Wedensky, and Ukhtomsky and past-Pavlovian developments in the study of conditioned reflexes are briefly considered.

It is in the second half of the book, however, that most readers will find subjects of greater interest. The three chapter headings "Brain Stimulation and Conditioned Reflexes," by Robert Doty; "Electroencephalographic Study of Conditioned Learning," by Frank Morrell, and "Electrical Correlates of Conditioned Learning," by Robert Galambos give but little concept of the wide variety of studies presented here by means of questionings and interpolations by various members of the panel. In general these studies are concerned, as Dr. Galambos states, with the search for "a neural basis for (*a*) the temporary connections of learning, (*b*) the innate connections that underlie motivation, and (*c*) attention." It is to the first of these objectives that greatest attention is directed at this conference. The methods used in general are three: (1) substitution of central stimulation for the conditional or unconditional stimulus, thus bypassing the peripheral receptor (as reported by Dr. Doty); (2) study of the central electrical response rather than a behavioral response (as detailed in Dr. Morrell's studies utilizing sound as the conditional stimulus and light as the unconditional stimulus); (3) recording of central electrical activity during the establishment of classical conditioned responses. The last method was demonstrated by Dr. Doty's evidence in cats of cerebral electrical arousal to a tone preceding an unavoidable shock, the arousal response becoming quite consistent before any motor response to the tone appeared; by Dr. Galambos' study of change in evoked potentials to a "click" when the sound is repeatedly associated with a shock, and by Dr. John's finding of frequency-specific responses in various regions of the brain when flickering light at specific frequencies was used as the conditional stimulus. In addition are included presentations of animal studies on self-stimulation by Dr. Lilly and self-injection by Dr. Olds and studies on arousal by Dr. Rowland. In fine, the second portion of this book abounds with glimpses into the many facets of work presently being carried out in this dynamic field.

From the standpoint of readability this book, probably owing to skillful editing and vigorous presentations, stands high among publications of conference proceedings. While one may occasionally be infuriated by interruptions (as when Dr. Brazier's discussion of Sechenov is interrupted by, "Is the portrait of Borodin in Moscow now? It used to be in Leningrad," or Dr. Leake's presentation by, "What was Dogiel's university connection? Was that Dorpat?"), these are rare—and for the most part they are pertinent and contributory.

The second volume, "Brain-Memory-Learning," by W. Ritchie Russell, is subtitled "A Neurologist's View." In essence it is an attempt to mold the concepts of Freud and Pavlov and a segment of modern neurophysiological thought into a unified concept of memory and learning consistent with the author's wide experience in clinical neurology. It is based essentially on his studies, which have continued over almost three decades, of the effects of brain injuries on cerebral function (twenty of the ninety-three references listed are by the author) when considered in the light of present-day concepts in neurophysiology, psychology, and psychoanalysis. If this volume is not entirely successful, it nevertheless certainly deals with a subject worthy of serious consideration by the clinical neurologist.

At the outset Dr. Russell states that the central theme of his book will be "the probable importance of tonic neural activity, coupled with the altered conditions of intercellular transmission to which it may give rise." From this emerges, as earlier conceived by Eccles, the formulation that individual nerve cells show a fundamental tendency to repeat actions which have occurred, this being evident in spinal cord reactions and being common to all nerve tissue. Thus the central nervous system "rarely neglects what it has learned but maintains what is learned by spontaneous discharges of cells concerned, which are 'exercising,' as it were, through the neuronal pattern established when the skill was first acquired." The characteristics of motor responses include transfer of strength of excitation to rate of discharge; a strong tendency for one response to be followed by another; timing of intervals at which consecutive motor responses should occur, and correlation of one motor response with another. These same qualities are thought to form the basis of human thinking and memory. Thus arises a scientific hypothesis to explain the importance for further development and behavior of learning in early life.

He introduces a helpful concept differentiating memory into two distinct phenomena—recognition (the "I've been here before" phenomena) and detailed recollection of past events—pointing out that these two properties do not necessarily go hand in hand, though one may be dependent upon the other. The chapters considering cerebral memory, concussion, and the traumatic amnesias are particularly good, dealing as they do with subjects with which Dr. Russell's name has long been identified and unifying many concepts which have appeared previously in separate papers.

In a book which attempts much within so small a space, obviously every reader cannot be entirely pleased. The last portion of the book, dealing with the search for the highest level of the brain, particularly with reference to man's highest integrative functions, is the least satisfactory. Although earlier the author had stated that "the levels are so interdependent that it is more reasonable to speak of the cortical contribution than the cortical level" and "it would be better, perhaps, to begin thinking of systems instead of levels," nevertheless he must "try to determine which system 'has the last word' in individual reaction and behaviour." The highest level he localizes to the frontal lobe-hypothalamic area—a not surprising hypothesis but one, in the reviewer's opinion, insufficiently documented in this brief study. Thus, "it is worthy of note that epileptic discharges originating in the frontal lobes commonly lead to instantaneous loss of consciousness—an impressive indication of the powerful nature of the frontal mechanisms." While assuredly this indicates the powerful nature of the mechanism, the abnormal function of epileptogenic neurons can hardly be accepted *quid pro quo* for normal function. While the importance of frontal lobes in mentation is not to be doubted, the evidence presented here, in this and other more detailed passages, does not convincingly prove their superiority in a hierarchical system. "There have been many attempts to upset the idea of a highest level in the brain, but in an efficient and sane individual there must be a mechanism which 'has the last word,'" but the author does not consider that in the individual conceivably there is no 'last word' in the sense of a neural mechanism to which decision and control are delegated. Perchance there is only an outcome predetermined by innumerable stimuli acting upon effector mechanisms. The book would have been stronger had the author abandoned a search for highest level, the evidence for or against which could not be adequately presented in a small volume, and been content to accept the interactions of various levels functioning in an integrated fashion.

In discussing two such dissimilar books in a single review, obviously there is hope that something can be gained by a dual consideration. The most striking thing noted in studying these volumes together is the hiatus which, in spite of concerted efforts on all sides, separates those who study in the basic sciences from those whose interests are basically clinical—or, in

more concrete terms here, the gulf separating those whose greatest endeavors lie in study of the lower animal kingdom and those whose proper interests lie predominantly in man.

Thus, in the conference, exciting as are the findings reported in a field in which developments are of particular significance at present, the reviewer was constantly struck by the absence of interest in the applicability of the studies for human behavior. Although Dr. Galambos does remark that in these procedures we ask animals simple questions and get simple answers, although Dr. Yakovlev reminds us that "when one deals with the hemisphere of a cat or dog, one really deals with rhinic and limbic lobes only," although occasionally there arises some mention of differing responses between lower animals and man—and, finally, although without doubt the object of the work of each of these investigators is to further understand the behavior of man in health and disease—still the gap separating these studies from studies on human behavior is considerable.

On the other hand, in Dr. Russell's book, concerning itself almost entirely with man, the difficulty lies in the opposite direction. Here the tools useful in the study of processes of memory and learning in lower animals are not seriously considered—indeed, none of the recent studies on conditioned cerebral responses are discussed, though, for example, the studies of Dr. John on tracer responses in animals might have bolstered Dr. Russell's contention regarding the tendency of neurons to repeat their previous actions. How much more might have been learned of his patients with cerebral injury had they been subjected to really exhaustive psychological evaluation, or had all aspects of their readjustment to home and society been pursued to the utmost extent!

These criticisms of the separation in approach between these two groups are in no wise condemnatory. They are, rather, meant to focus attention to the loss of our knowledge of man which inevitably follows such separation and the rewards which might be reaped by continued endeavors to bridge this separation.

CHARLES E. WELLS, M.D.

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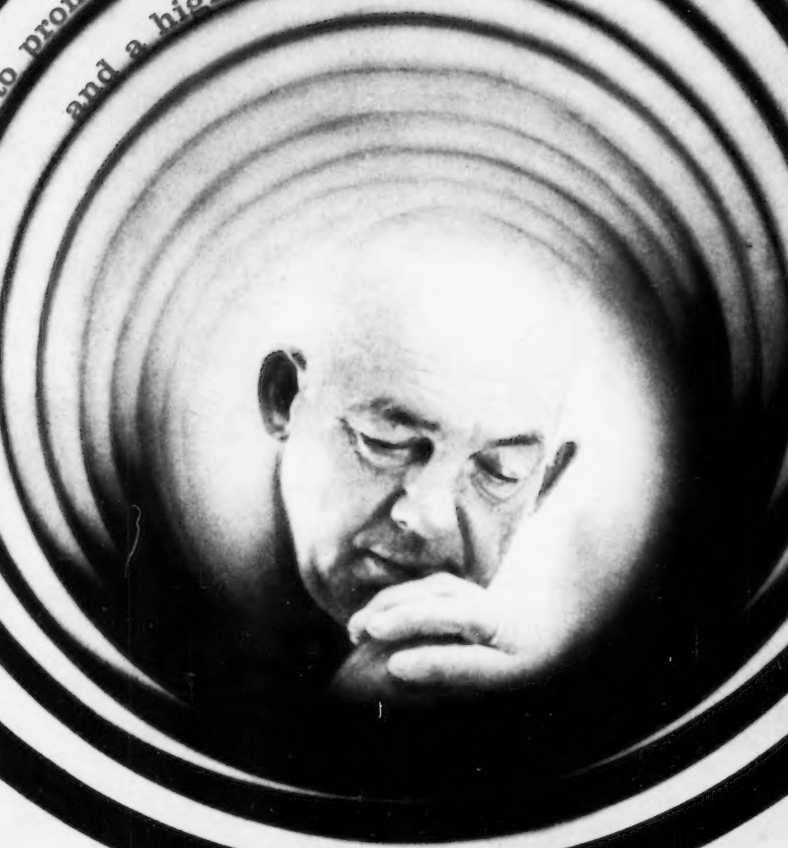

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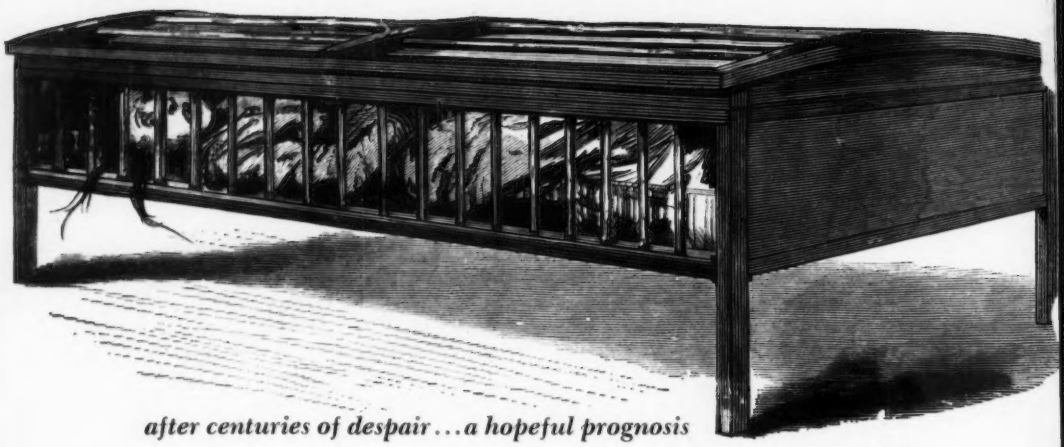

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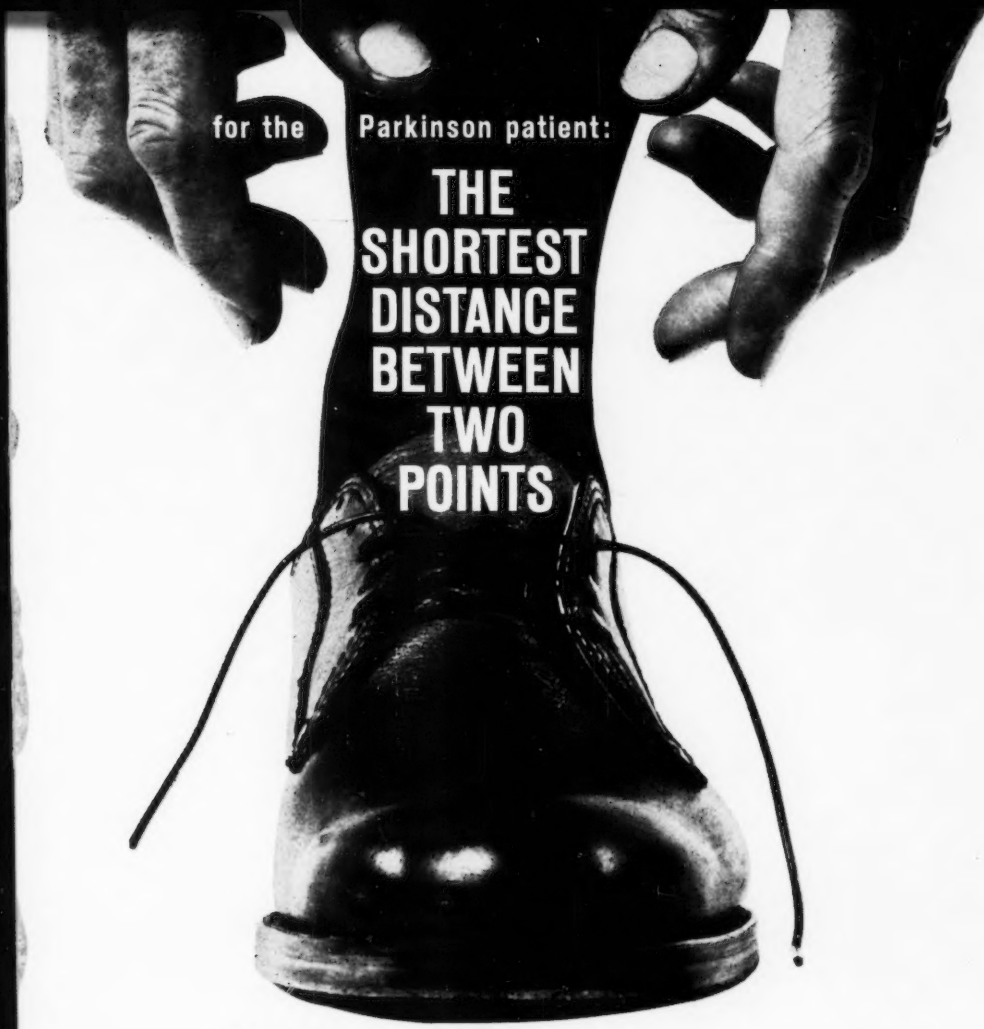

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1. Doshay, L. J.: M. Clin. North America 40:1401 (Sept.) 1956.
2. Doshay, L. J.: Current M. Dig. 22:11:49 (Nov.) 1955.
3. De Jong, R. N.: J. Michigan M. Soc. 57:722 (May) 1958.

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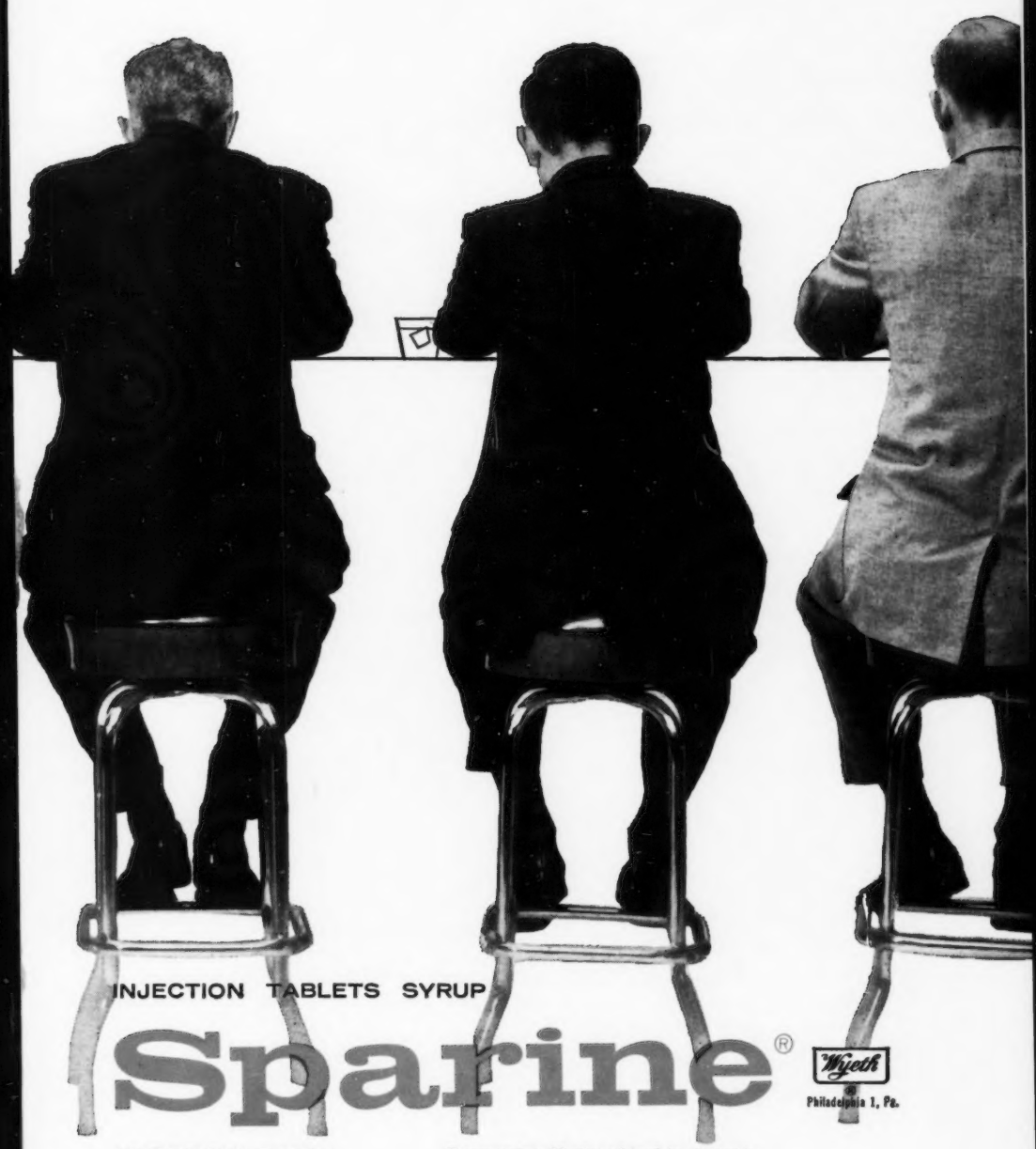

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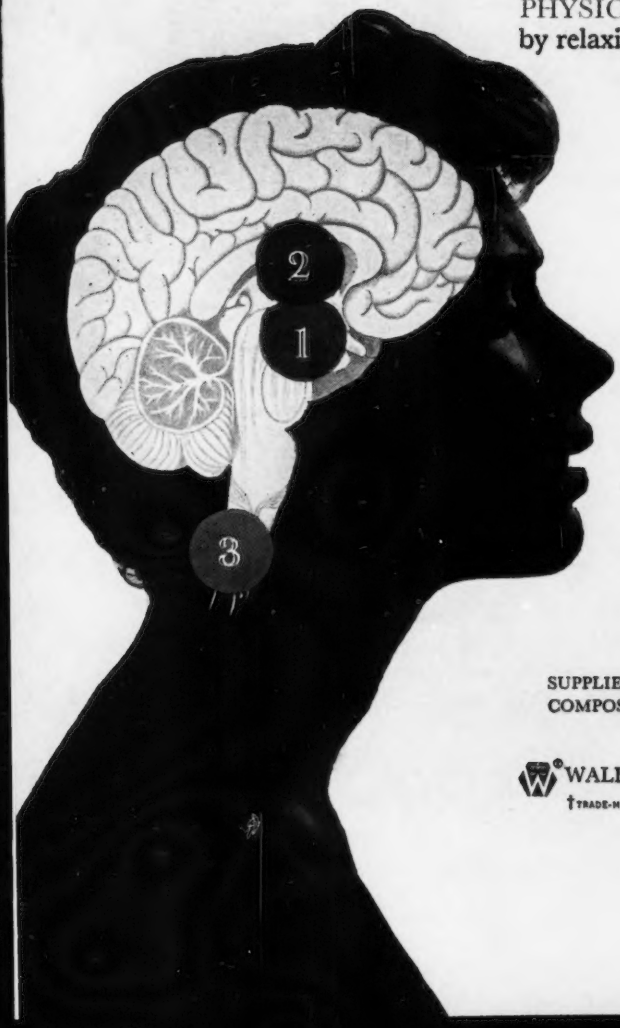

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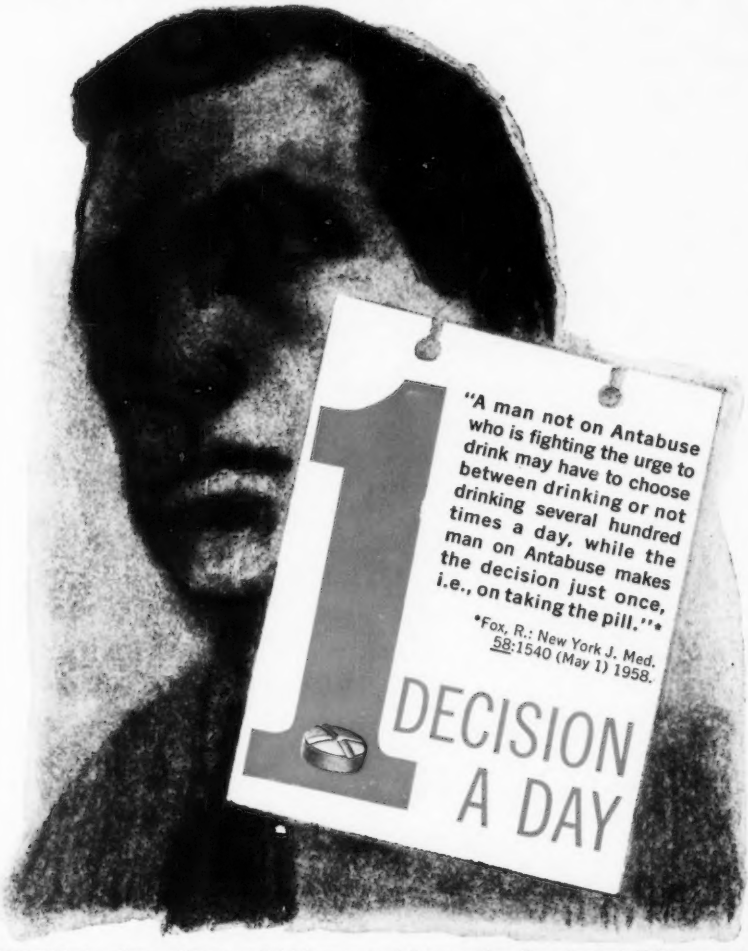
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1. Ayd, F. J., Jr.: Bulletin of School of Medicine, University of Maryland 44:29, 1959. 2. Azima, H.: Canad. M. A. J. 80:535, 1959. 3. Azima, H., and Vispo, R. H.: Am. J. Psychiat. 115:245, 1958. 4. Kuhn, R.: Am. J. Psychiat. 115:459, 1958. 5. Lehmann, H. E.; Cahn, C. H., and de Verteuil, R. L.: Canad. Psychiat. A. J. 3:155, 1958. 6. Mann, A. M., and MacPherson, A. S.: Canad. Psychiat. A. J. 4:38, 1959. 7. Sloane, R. B.; Habib, A., and Batt, U. E.: Canad. M. A. J. 80:540, 1959. 8. Straker, M.: Canad. M. A. J. 80:548, 1959.

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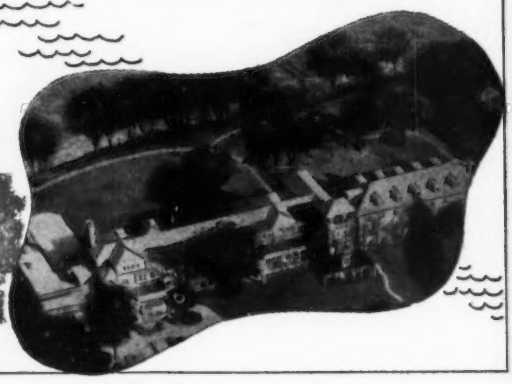

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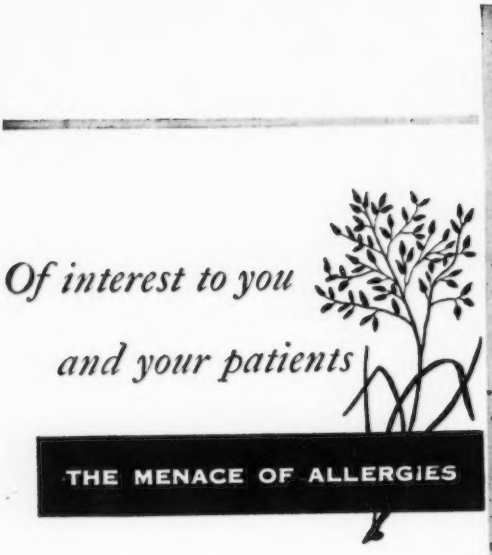

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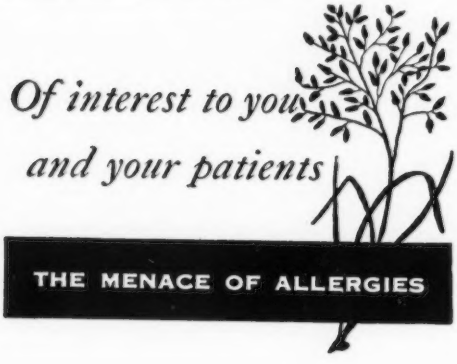

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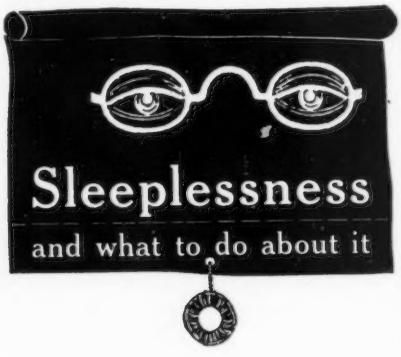

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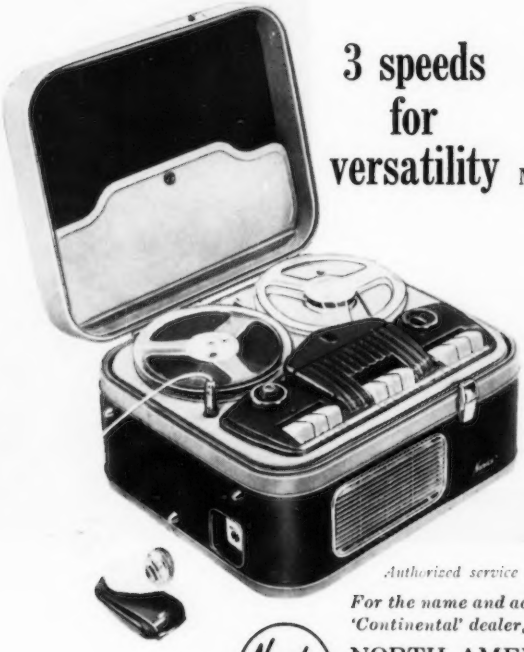

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